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AN EXPERIMENTAL INVESTIGATION OF THE PHARMACOLOGIC PROPERTIES OF THE ACTIVE PRINCIPLE OF COMMERCIAL PITUITARY EXTRACTS, AND OF THE COMPARATIVE ACTION OF HISTAMINE*

BY D. E. JACKSON, M.D., AND C. A. MILLS, B.A., CINCINNATI, OHIO

SOME years ago while performing some experiments on the lungs, one of us observed what appeared to be a notable difference between the action of pituitrin and that of histamine ("ergamine," β-iminazolylethylamine) on the bronchioles of the dog. The later adoption of histamine in the U. S. Pharmacopœia as a standard to be used in the testing of commercial preparations of the infundibular portion of the pituitary gland served to again call attention to the previous (unpublished) observation. And during the progress of the work here reported, the publication of an especially interesting and valuable article by Abel and Kubota[1] has again served to add interest to the work.

The literature on this subject is very extensive, but we need to refer here in detail to only a few articles. A very comprehensive review (also bibliography) of the current knowledge of the action of extracts of the hypophysis has recently been published by Houssay[2] in his excellent monograph on that subject. McCord,[3] Roth,[4] Hamilton and Rowe,[5] Dale and Laidlaw,[6] Barger and Dale[7] and Abel and Kubota[1] (bibliography) have also made very valuable contributions to that phase of the subject with which we are especially interested in this article.

Figure 1 illustrates graphically the nature of the observation originally made with reference to the relative action of *commercial* "pituitrin" (Parke, Davis & Co.) and that of histamine ("ergamine" of Burroughs Wellcome &

*From the Department of Pharmacology of the University of Cincinnati Medical School, Cincinnati, Ohio.

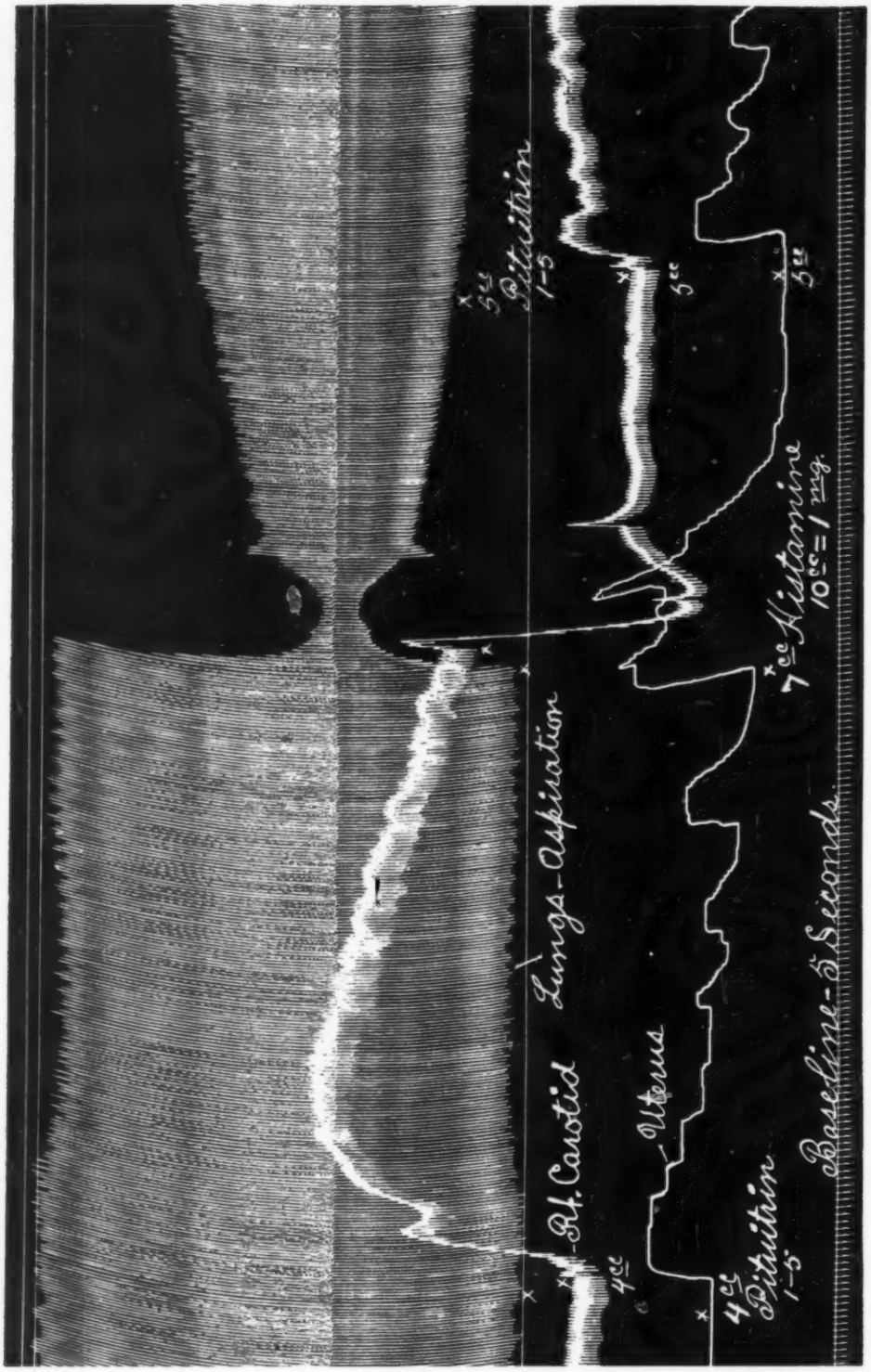

Fig. 1.—For discussion see text.

Co.). In this tracing a pithed dog of 7.2 kilos weight was arranged for the recording of uterine contractions (uterus in situ), blood pressure (mercury manometer, right carotid artery), and bronchiole contractions. The method[9] used in recording the latter has been fully described previously and need not be discussed here further than to briefly indicate that a special instrument (lung plethysmograph) was inserted air-tight into the sectioned anterior wall of the chest. This instrument held the chest wall rigidly expanded and a special artificial respiration machine was used to aspirate air from the chest intermittently. This partial exhaustion of the chest cavity caused air to rush into the lungs through the trachea and expand the lungs. The drum tracing was made by means of a tambour connected to the side tube of the tracheal cannula. The record thus obtained shows by its amplitude the amount of air passing into and out of the lungs at each inspiration and expiration. Contraction of the bronchioles reduces this amount of (tidal) air and simultaneously reduces the amplitude of the lung tracing.

In Fig. 1 it is seen that the intravenous injection of 4 cubic centimeters (from a burette into the femoral vein) of a 1 to 5 dilution of Parke, Davis & Company's *commercial* pituitrin caused a contraction of the uterus, a very considerable and prolonged rise in blood pressure, but scarcely any appreciable effect on the bronchioles. Whatever effect the tracing may show in this case on these we believe to be due entirely to some obscure changes in the volume of blood in the lungs (thus probably slightly changing their degree of elasticity), or to changes in the relative dilatation of the heart. In this case we believe that no true contraction of the bronchial musculature due to a direct action of the pituitrin occurred.

After the effects of the pituitrin had mainly worn off another injection of 7/10 of one milligram of histamine (ergamine) was made. This produced a more marked contraction of the uterus, a sharp fall in blood pressure and a considerable contraction of the bronchioles. This contraction of the bronchial musculature tended to pass off but slowly, so that a later injection of 5 cubic centimeters of pituitrin (1 to 5) was made in order to determine whether or not the pituitrin would counteract the action of the histamine. This produced contraction of the uterus and a rise in blood pressure, but no perceptible increase in the previous slow rate of dilatation of the bronchioles. Obviously this indicates that *commercial* pituitrin does not possess much power toward counteracting the constricting influence of histamine on the bronchioles.

It would appear that certain conclusions might be drawn from this experiment, but we have refrained from proceeding too hastily in the matter in the hope that a variety of experiments might throw a different light on the problems here involved. We may, therefore, refer to Fig. 2 in which two (separate) tracings, both taken from the same animal, are shown. Here a contraction of the uterus in situ was produced in the first case by 1/15 of a milligram of histamine (ergamine). This is practically 1/15 of the ordinary therapeutic dose of this material as placed on the market in hypodermic tablets by the Burroughs Wellcome Co. The second part of the tracing shows a contraction of the uterus produced by 1/2 cubic centimeter of pituitrin (Parke, Davis & Co.) diluted 1 to 5 with distilled water. Both injections were made into the femoral vein. In

both instances the uterus was relaxed (after a brief primary contraction) by the injection of 1/4 cubic centimeter of adrenaline (1 to 10,000). These two tracings show that 1/15 of a therapeutic "dose" of histamine produced a little greater contraction of the uterus in this particular animal than 1/10 of a therapeutic "dose" of pituitrin. While these "doses" are not sufficiently accurate to serve as a basis for exact scientific conclusions, they are still useful here as a means of giving some approximate estimation of the relative activity of different amounts of the two substances on the uterus in situ in a dog in which the organ (in this instance) was especially sensitive to both drugs. By comparison with Fig. 1 it will be seen that in that tracing 8/10 of a therapeutic "dose" of pituitrin caused a somewhat less contraction of the uterus than did 7/10 of a "dose" of histamine. But the action on the bronchioles is quite different in these two instances. That the injection of pituitrin in this case (4 c.c. of 1 to 5 dilution)

Fig. 2.—For discussion see text.

was sufficient to elicit the ordinary pharmacologic reaction of the drug is shown by the very marked rise in blood pressure.

A variety of methods and of animals have been used by previous workers in studying the action of pituitary extracts on the bronchioles. The conclusions of these observers may be briefly summarized as follows: P. Titone,[10] working with isolated bronchial muscle, found no action produced by hypophysin and pituitrin. In guinea pigs, Froehlich and Pick[11] found pituitary extracts to produce fatal broncho-spasm which they believed was of peripheral origin and could be prevented by atropin, while in perfused guinea pigs' lungs Baehr and Pick[12] found that after perfusion with pilocarpine and adrenaline the later perfusion of "pituglandol" (Hoffmann-LaRoche—4 c.c. per 100 c.c. Tyrode's solution) through the lungs for 20 minutes failed to contract the bronchioles, while immediately following this, perfusion with histamine (1 mg. to 100 c.c. Tyrode) caused broncho-spasm in one minute, and this was relieved by perfusion with adrenaline (1 to 100,000) for two minutes. But in a freshly prepared animal

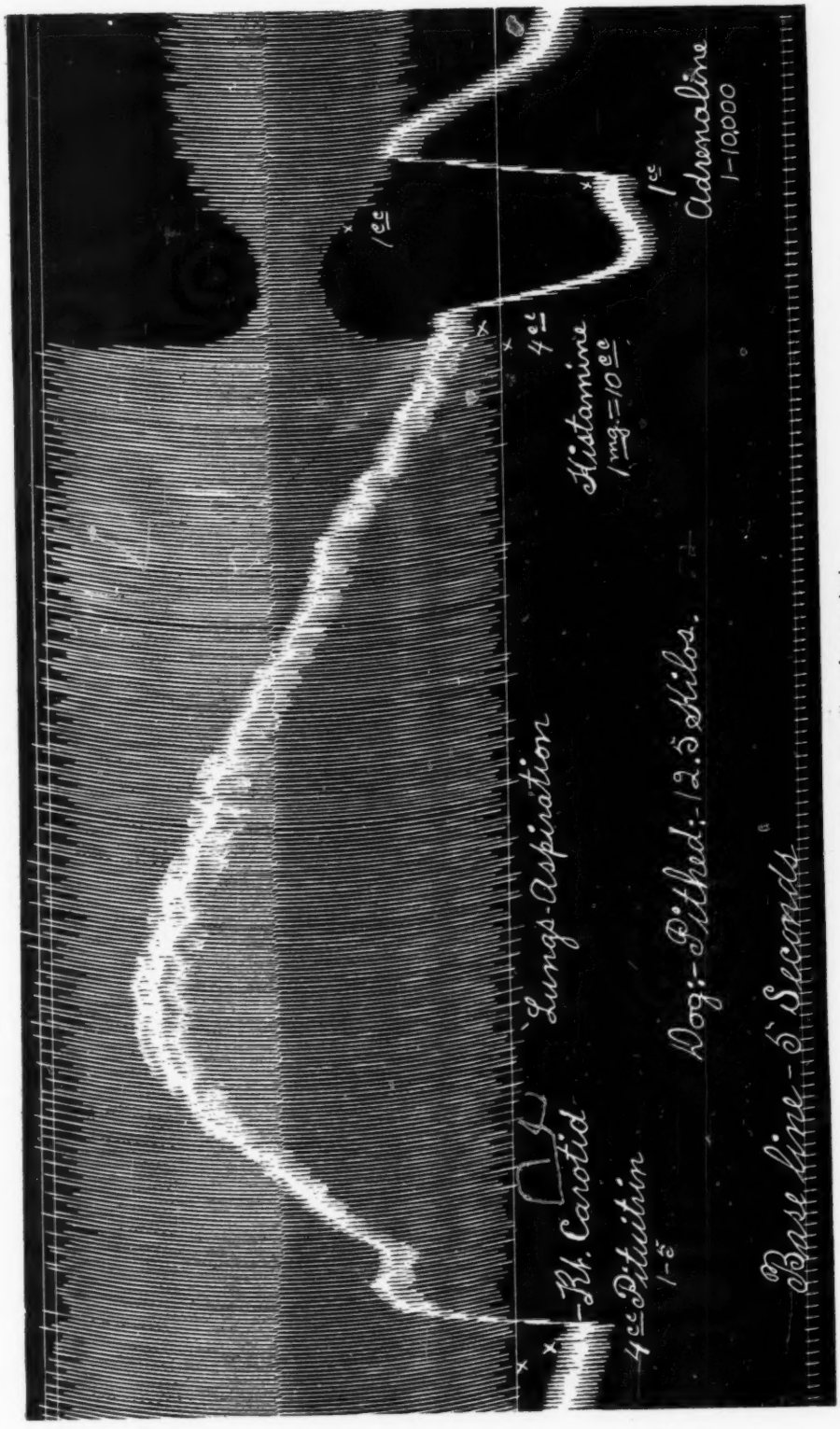

Fig. 3.—For discussion see text.

pituglandol produced bronchoconstriction (Lungenstarre) after a short time. Houssay[13] observed bronchoconstriction in guinea pigs, while Borchardt[14] and Bourgeois[15] have attempted to use pituitary extract in the treatment of bronchial asthma, and Zueblin,[16] and Bensaude and Hallion[17] have studied the action of the combination of pituitrin and adrenaline in asthma. Lanari[18] has induced asthmatic attacks by the administration of pituitary extract. Jackson[19] has published (without discussing) a tracing showing a contraction produced in the lungs of a turtle by the injection of pituitrin into the circulation (heart), and another tracing showing a slight bronchoconstriction in a dog when a dose of 5 c.c. of pituitrin (1 to 5) was injected intravenously. Both of these results have already been quoted in the literature[20] as evidence that pituitary extracts will produce bronchoconstriction.

It will thus be seen that the literature is somewhat inconsistent with reference to the action of pituitary extracts on the bronchi. Regarding the action of histamine on the bronchi, however, there is no difference of opinion.

In Fig. 3 are shown the comparative actions on the bronchi and blood pressure of 4 c.c. of pituitrin (1 to 5) and 4 c.c. of histamine solution (4/10 mg.). In the recent paper by Abel and Kubota the interesting suggestion is made that the plain muscle stimulating and depressor constituent of the posterior portion of the pituitary gland is really histamine. We have kept this valuable suggestion in mind while we have been carrying out a portion of this work. The very considerable financial gain to laboratory and clinical workers which observations of this kind foreshadow is a matter of much interest to all. And we have performed some experiments with the special object of studying the comparative action of pituitrin and histamine on the bronchi in order to gain as much light as possible regarding the presence of histamine in ordinary *commercial* preparations of the pituitary gland. While the foregoing experiments indicate that the pituitary extracts possess practically no action on the bronchi either in the line of contraction or dilatation, we must state, however, that with some of the commercial products the presence in minute quantities of some substances possessing a histamine-like action is very evidently indicated. We have felt that this could best be demonstrated by introducing a number of tracings showing a gradual gradation from practically no effect at all on the bronchi to a rather marked bronchoconstriction.

Figure 4 shows an injection of 3 c.c. of pituitrin (1 to 5) which produced a marked uterine contraction, a considerable rise in blood pressure, but practically no effect on the bronchi. The slight shortening of the amplitude of the lung tracing here is almost certainly due to blood volume changes in the lungs, or to the action of the drug on the heart (McCord.) In this case, as in Fig. 1, the conclusion might easily be drawn that the uterine contracting and the blood pressure raising substance was one and the same. But on the other hand it might be supposed that histamine present in the commercial pituitrin was responsible for the uterine contraction and that the blood pressure raising principle was powerful enough to overcome the action of the histamine on the blood pressure. But it has been shown in Tracings 1 and 3 that the bronchioles are exceedingly sensitive to very small amounts of histamine (much more sensitive than is the uterus in dogs). In order to explain the failure of the pituitrin to contract the bronchi in Fig. 4 then, it might

be presumed that the pressor substance stimulated the endings of the broncho-dilator nerves (sympathetic) and thus counteracted the direct muscular constricting action of the histamine. We might suggest here that atropine does not change any of these reactions, so that the vagus nerve is probably not concerned in them. The later failure of adrenaline to cause any perceptible dilatation of the bronchi in Fig. 4 shows that no special contraction had been produced by the previous pituitrin injection. (This very slight progressive shortening for a

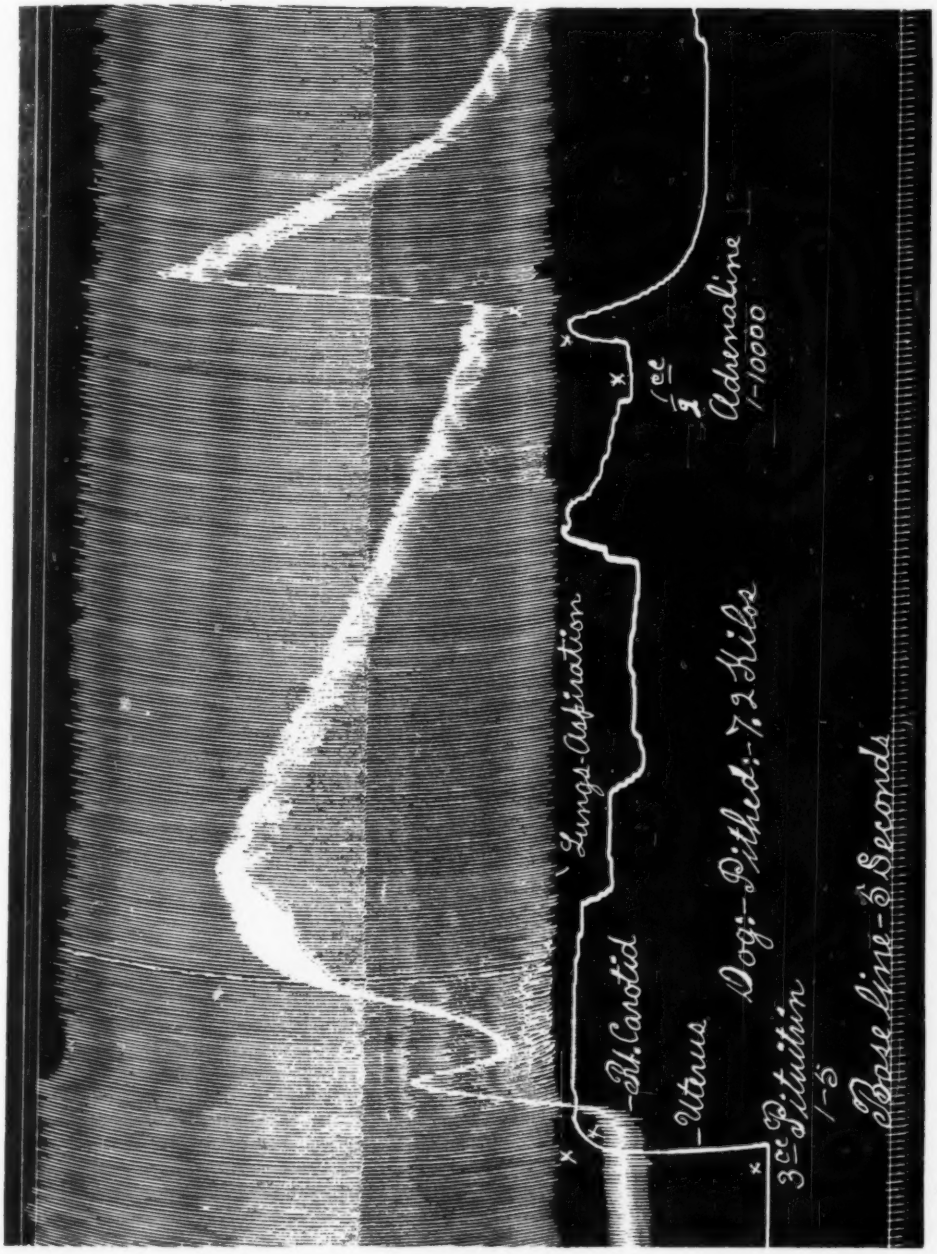

Fig. 4.—For discussion see text. When the blood-pressure rose there was a very slight interference between the writing point of the manometer and that of the lung tambour. The tambour was accordingly moved slightly to the right.

time in the amplitude of the lung tracing is often seen with this method in normal animals, when no drugs at all are given.)

Figure 5 shows a slightly different type of action. In this case 2½ c.c. of infundin (Burroughs Wellcome & Co—1 to 5 dilution) were injected and caused a marked effect on the blood pressure. This evidently consisted of a mixture of pressor and depressor effects. The heart was evidently also involved in this (the medullary centers were, of course, not concerned, as the brain and most of the cord were destroyed). But in this case there is more evidence of a bronchoconstrictor action. It is perhaps observable here that the most marked period of bronchoconstriction coincides with the position of the greatest

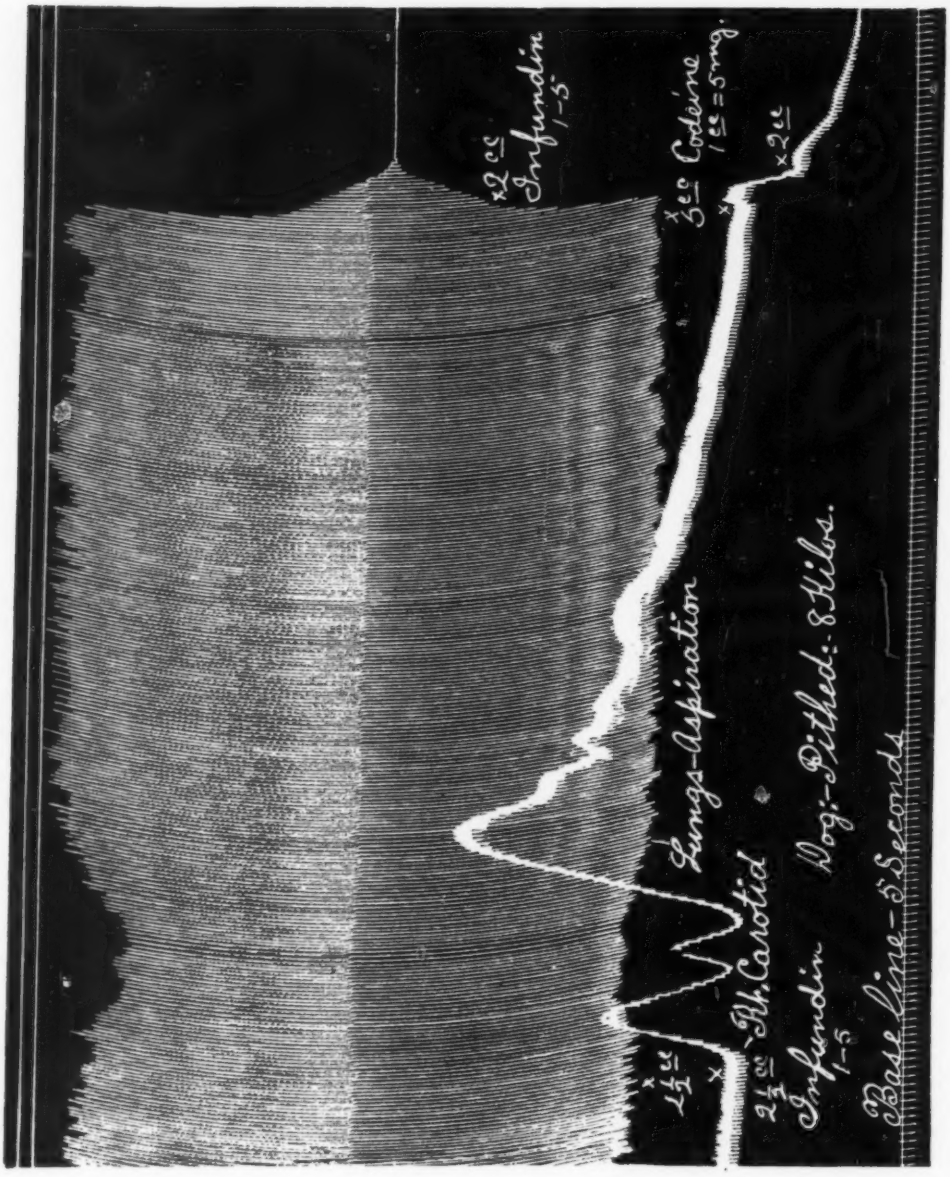

Fig. 5.—For discussion see text.

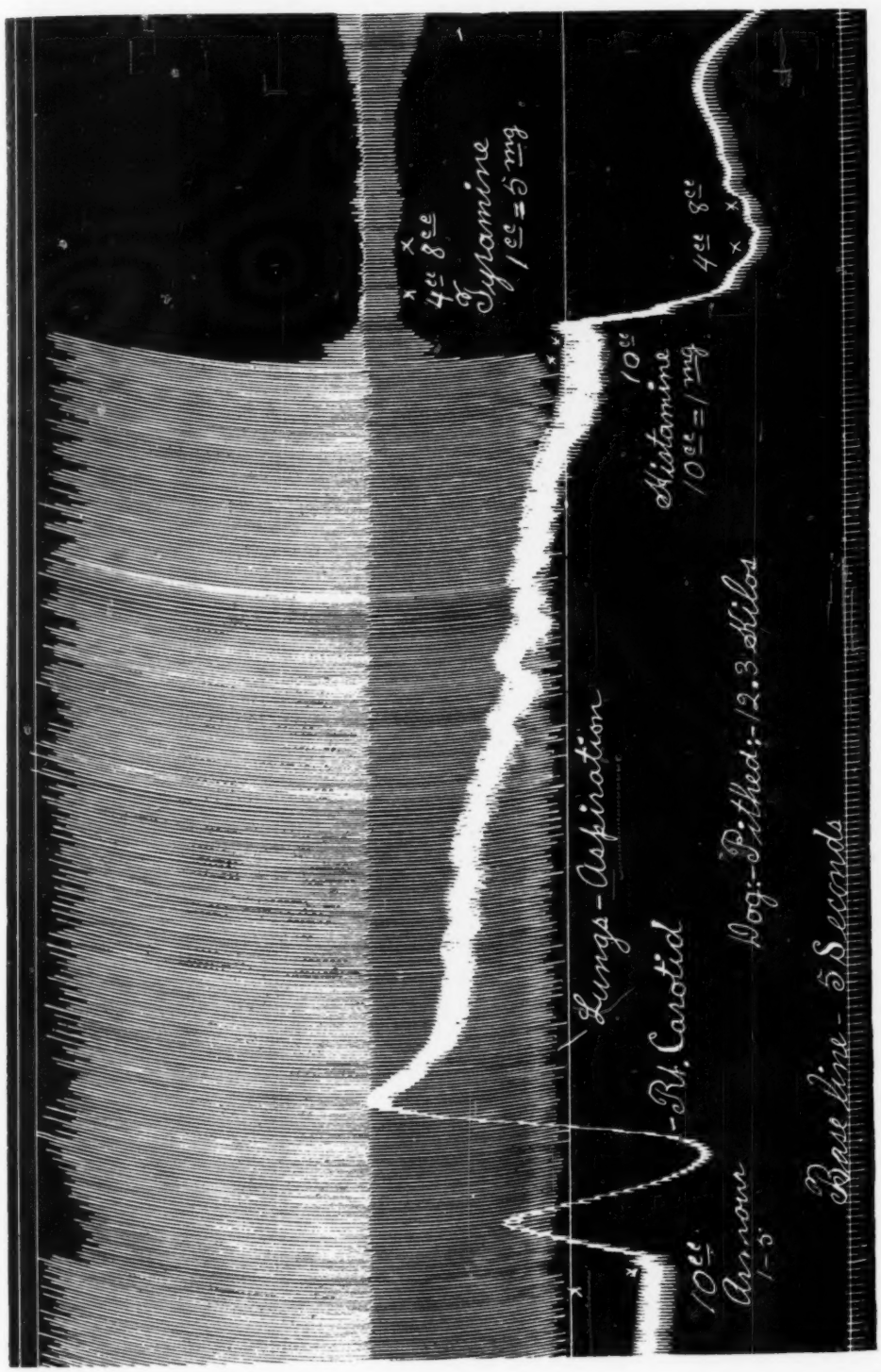

Fig. 6.—For discussion see text.

Fig. 5.—For discussion see text.

fall in blood pressure. We have observed this same point many times. But coinciding with the point of greatest rise in blood pressure in the tracing there appears to be a fairly evident dilatation of the bronchi. This may be due to the better circulation washing out any constrictor substance which might have been acting on the lungs. Or it might be due to the pressor substance stimulating the bronchodilator nerves. This possible action of pituitary extracts to dilate the bronchioles we have kept carefully in mind, as it might entirely explain the difference in action on the bronchi between pure histamine and pituitary extracts. We have therefore devised several experiments to test this point. Consequently in the last part of Fig. 5 we injected 25 milligrams of codeine sulphate to produce a bronchoconstriction (direct muscular effect), and then attempted to inject 2 c.c. of infundin (1 to 5) to determine whether or not the extract could cause an active bronchodilatation. But the dose of codeine was too large for this animal which was evidently exceedingly sensitive to substances producing a direct muscular stimulation of the bronchi. Consequently no conclusions could be drawn here regarding a possible dilator action of the infundin. By reference to Fig. 1, however, it will be seen that 5 c.c. (1 to 5) after the injection of histamine failed entirely to produce any active increase in the slow rate of relaxation of the bronchi.

In Fig. 6, ten c.c. of Armour's "pituitary liquid" (1 to 5 dilution) were injected. Two phases to the blood pressure changes are markedly produced (see McCord: Arch. Int. Med., 1911, viii, 609). A notch is also formed in the top of the lung tracing. This does not, however, have quite the appearance of a true bronchoconstrictor effect, but rather seems due to other causes which are almost certainly connected with the circulation. Later in the tracing 1 milligram of histamine is injected and this is followed by two injections of tyramine, the object being to determine whether or not this body (which Abel and Kubota have suggested may be quite similar to the pressor principle in pituitary extracts) could cause a dilatation of the bronchi sufficiently powerful to prevent a histamine contraction if both histamine and tyramine (para-hydroxyphenylethylamine) should be acting in combination at the same time on the lungs. In this experiment the dilator action of tyramine (Burroughs Wellcome & Co.) was entirely too feeble to overcome the bronchoconstriction produced by the histamine. Possibly it might be questioned here whether or not the proper doses had been selected to give a fair test to the combination as it (histamine plus some unknown pressor body) might exist in pituitary extracts. The proportion of histamine to tyramine here was 1 to 60, but we have tried a variety of other proportions of this combination both when the drugs were injected separately and when mixed before injection. It might be mentioned here that Baehr and Pick[21] have described a bronchoconstriction as being produced in perfused guinea pigs' lungs by tyramine dissolved in Tyrode's solution. Amyl nitrite removed this constriction. One of us has previously observed that tyramine caused a slight bronchodilatation in dogs (Jour. Pharm. and Exper. Therap., 1913, iv, p. 307) and we have confirmed this observation again in this work.

In Fig. 7, two c.c. of pituitrin, *full strength* (i.e., two maximum human doses for hypodermic injection) were injected intravenously into a small dog. The usual blood pressure reactions occur, but in addition there is a moderate

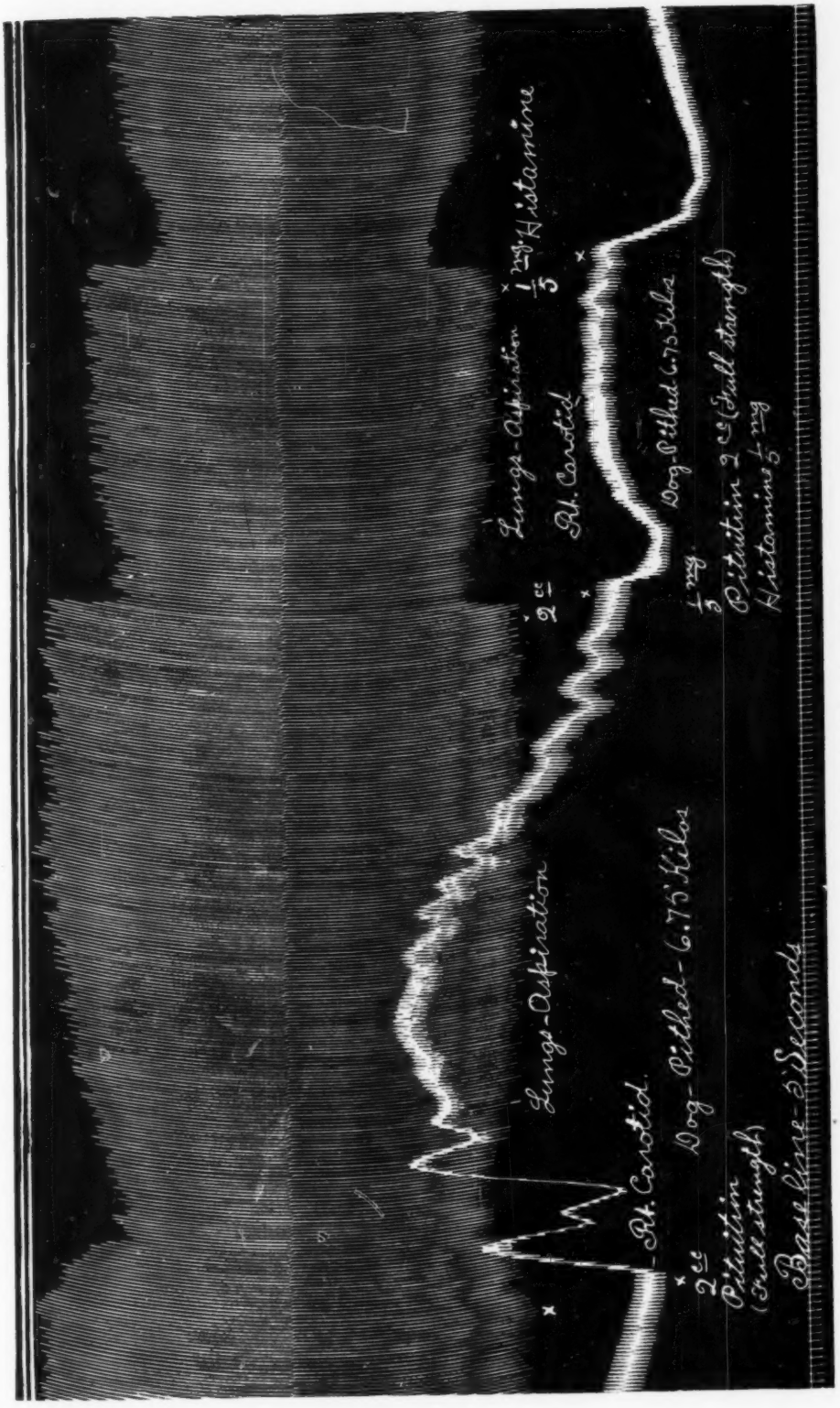

Fig. 7.—For discussion see text.

bronchoconstriction. Again this constriction coincides with the point of fall in blood pressure after the first primary rise. The character and general appearance of this bronchoconstriction should be directly compared with that produced by the second injection into the animal of 2 c.c. of pituitrin (same as the initial dose) but to which 1/5 of a milligram of histamine had been added before the pituitrin was injected (by means of a hypodermic syringe into the intact femoral

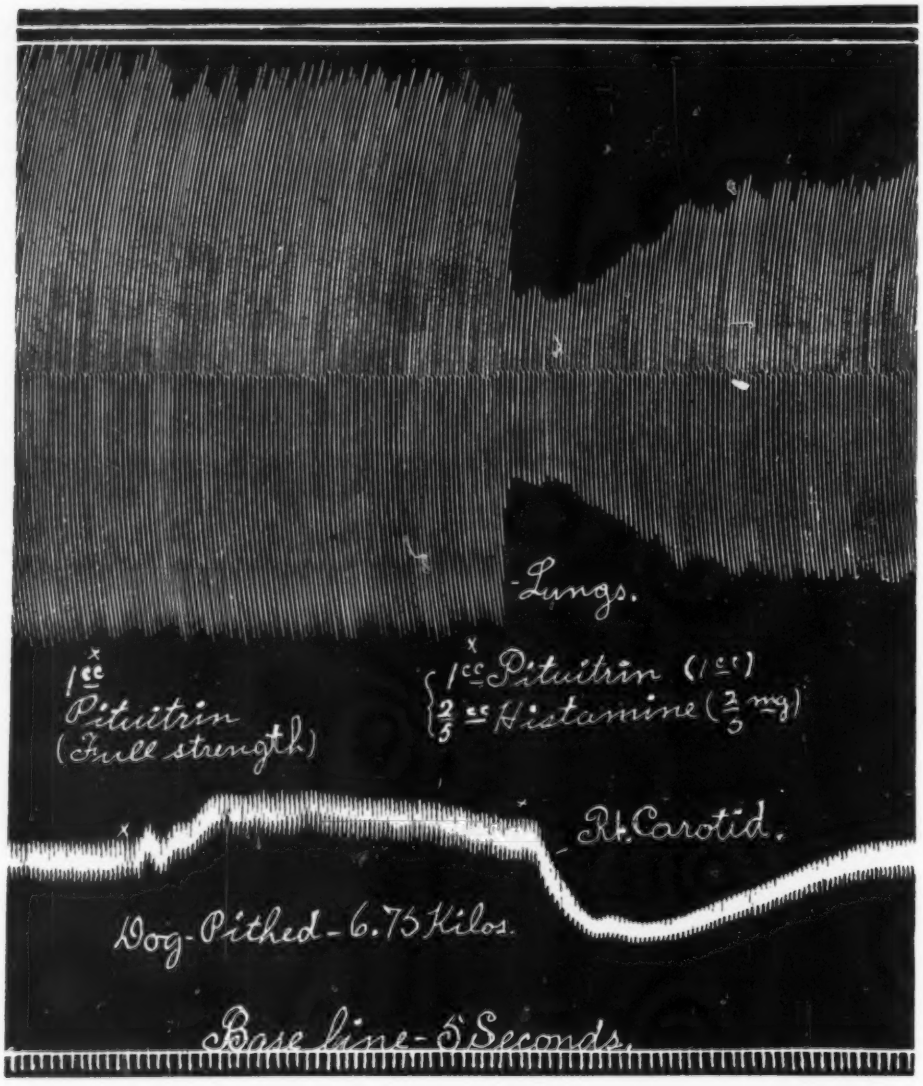

Fig. 8.—For discussion see text.

vein). Here a moderate, abrupt, and rather persistent bronchoconstriction is produced. In this case it might be suggested as possible that the pituitary pressor principle tended to counteract the bronchoconstrictor action of the histamine and thus reduced the normal action of the histamine on the bronchi. To further test this point we next injected 1/5 milligram of histamine (same as previous

dose) again. But the bronchoconstriction produced in this case is almost identical both in form and extent with that produced by the combined dose of histamine and pituitrin. We have considered the possibility that histamine might be loosely combined in some unknown fashion with the pressor principle of the pituitary extract. In this case it would be necessary to presume that some tissues (uterus, e.g.) could suddenly break down this combination and react to the liberated histamine while perhaps not responding to the pressor principle. On the other hand we should then be compelled to assume that the bronchioles of the dog possessed practically no power either to break down the combination or to react to the combination as a whole. This explanation does not seem very plausible to us, but it might be considered by others. And we are inclined to believe that Fig. 7, in which a mixture of pituitrin and histamine exercised practically exactly the same action on the bronchioles as a separate dose of the same amount of histamine alone, shows exactly the nature of the reactions here involved. It is to be noted that in this experiment very large doses of pituitrin are used. This was done in order to determine whether or not the doses ordinarily used were simply too small to produce bronchoconstriction. This suggestion probably involves an element of truth as later tracings will show.

Figure 8 is taken from the same animal as Fig. 7 and follows it directly. (The bronchi were in the meantime dilated back to normal by mechanically increasing for a moment or two the force of aspiration from the chest. The previous force of aspiration was then resumed.) In this tracing (8) one c.c. of pituitrin (*full strength*) is injected. The bronchial effect is exceedingly slight. This is followed by a second injection of 1 c.c. of pituitrin to which 2/5 of a milligram of histamine had previously been added. The bronchoconstrictor effect is almost exactly twice that which was produced by the two previous injections (Fig. 7) each amounting to one-half as much histamine as that given in Fig. 8. A further point should be noted here. The first injection of pituitary extract into an animal often gives a suspicious-looking bronchial tracing which might at once be taken to indicate a very mild degree of contraction. Later injections may, however, especially if they be of only ordinary quantities, show no trace whatever of a bronchoconstriction. By comparison of Figs. 7 and 8 it will also be seen that whereas the pressor effect of pituitrin tends to become less and less with repeated injections, the bronchoconstrictor effect of the same sized doses (or larger ones) of histamine tends to remain almost exactly the same. If ordinary commercial preparations of the pituitary gland are mixtures of histamine and some unknown pressor substance, then when repeated doses of commercial pituitary extracts are injected into dogs, and the pressor effects are gradually lost, then the response of the bronchioles to the histamine should probable become more and more relatively accentuated. This gives the pressor principle the benefit of the doubt as to whether or not it (if it could act alone) would possess a dilator action (as would be expected from the nature of its reactions on the blood vessels) on the bronchi, and assuming that the point of action of the substance here lost its susceptibility to the drug simultaneously as the pressor effect was lost. We do not think this is very probable, and experimentally the slight initial bronchoconstriction sometimes produced by ordinary doses of "pituitrin" rather tend to become less with repeated injections (and are very generally entirely ab-

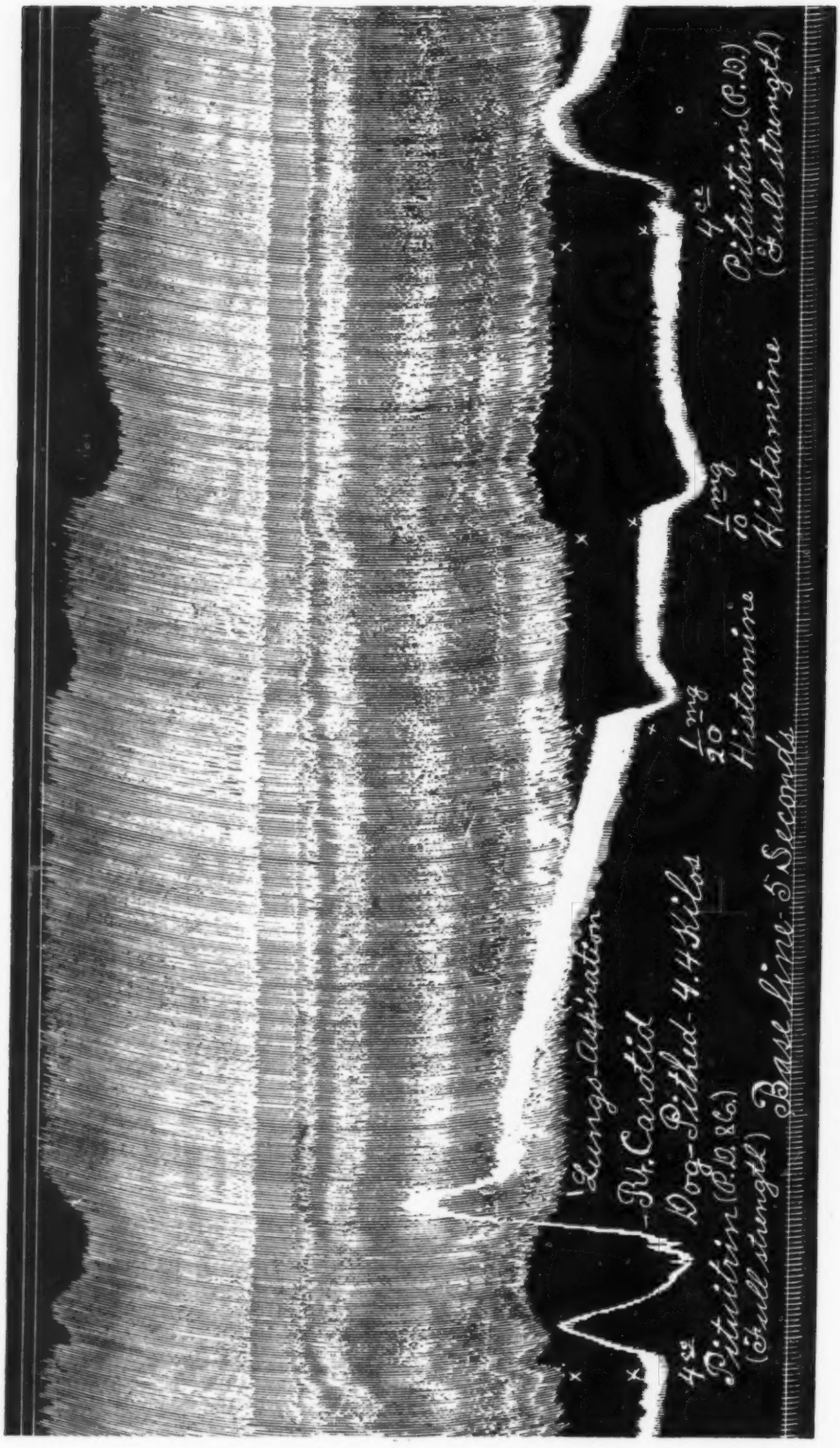

Fig. 9.—For discussion see text.

sent after the first dose). This leads us to suggest that we believe that the circulatory reactions to the drug are entirely responsible for such slight bronchoconstrictor effects as moderate doses of ordinary extracts may produce.

In Fig. 9 an enormous dose (4 c.c., full strength) of pituitrin was injected into a very small dog. The direct object here was to test the effect of large doses on the bronchi. The point which we had in mind was the possibility that a very small amount of histamine might be contained in these extracts. If this were the case a very large dose might contain enough to cause a bronchoconstriction. In this case the 4 c.c. did cause some bronchial contraction, and we are not sure as to the nature of this. We believe that the vascular changes probably account for most of the constriction. But there is a small, sharp notch just at the beginning of the contraction which looks very much as though it *might*

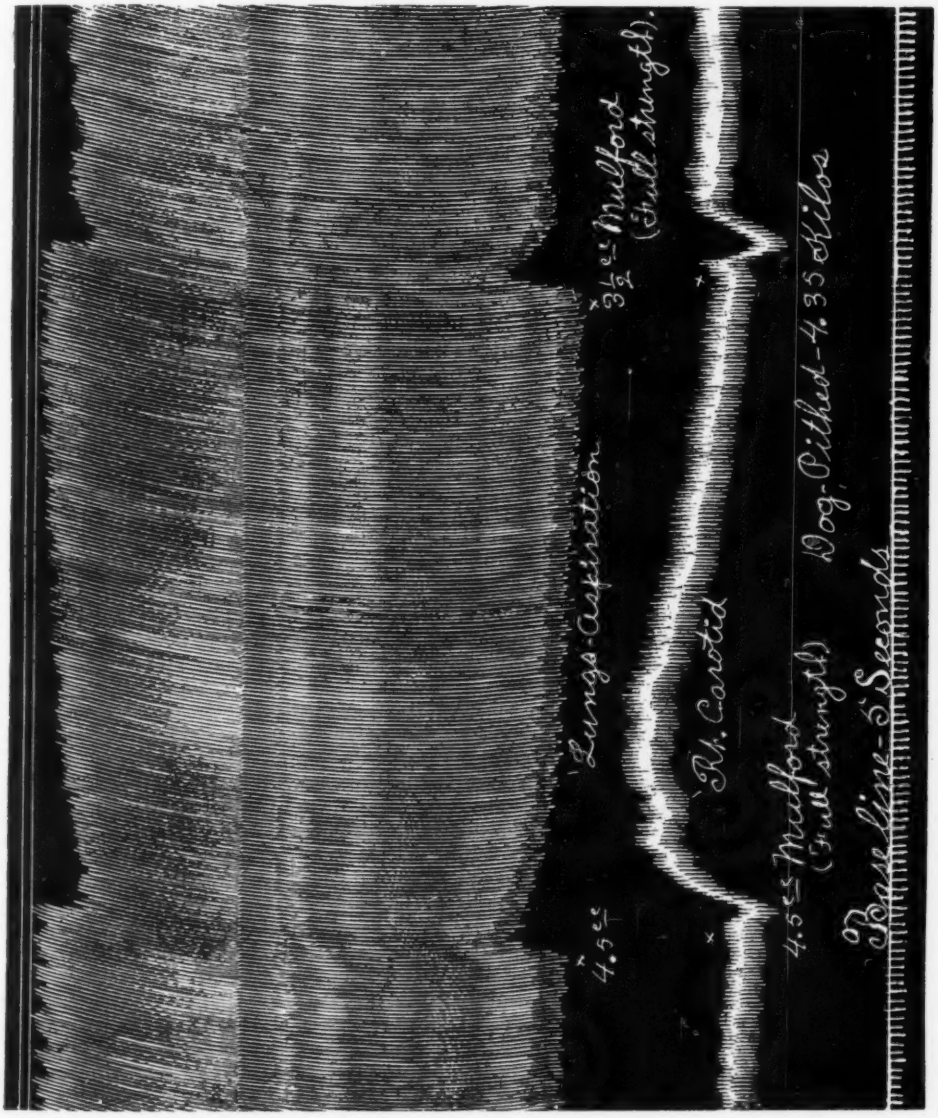

Fig. 10.—For discussion see text.

have been caused by a very small dose of histamine. To gain further light on this point we later gave two separate injections of 1/20 milligram and 1/10 milligram of histamine. The effects of these on the bronchi are quite obvious, and by comparison of all three injections we should estimate that the *apparent bronchoconstriction* produced by the 4 c.c. of full strength pituitrin corresponded approximately to about what we should have expected from a dose of 1/15 milligram of histamine at that stage of the experiment, i.e., there is indicated a bare possibility that each cubic centimeter of the pituitrin may have contained about 1/60 milligram of histamine. This gives the view that this sample of *commercial pituitrin* might contain histamine the benefit of all doubt in the matter, and we have proceeded from this point to reason as to whether or not this very small proportion of histamine could account for all the (histamine-like) therapeutic actions which the pituitrin is believed to possess. It is with a certain sense of regret that we have been compelled to conclude that the evidence is too small to substantiate the point. And it is interesting to observe that a second injection of 4 c.c. of full strength pituitrin following shortly after the last injection of histamine produced rather dilatation than contraction of the bronchi.

Figures 10 and 11 were both made in direct succession from the same animal. The primary injection into the animal was 4½ c.c. of Mulford's pituitary extract, full strength. The animal weighed only 4.35 kilos and both the brain and the entire cord were fully destroyed (eliminating all central influence). The animal had been etherized, but much of this had escaped before the first injection was made so that the presence of ether did not influence the tissues. The first injection raises the blood pressure (note the slight initial fall) and causes a direct and unmistakable contraction of the bronchi. A second injection of only 3½ c.c. of the same preparation caused a greater initial fall of pressure followed by only a slight rise. This shows quite well the usual loss of susceptibility of the vascular system to repeated doses of pituitary extracts. This second injection, however, produces a very evident and persistent contraction of the bronchi. And this contraction with a smaller dose than the first is more marked on the bronchi than is the constriction produced by the first injection. Evidently the substance which produces the bronchoconstriction does not simultaneously produce a loss of susceptibility as occurs with the pressor effect, but rather the reverse.

Passing now at once to Fig. 11 we see the result of the third injection into the animal of 3¾ c.c. (full strength) of the pituitary preparation sold by Heister. This produces a considerable rise in blood pressure, but without any special initial fall. We might suggest here that a great preponderance of pressor effect probably overcame the slight tendency for a primary fall which was almost certainly present. A slight but unmistakable bronchoconstriction is produced, but this is slightly less than that produced by a somewhat smaller dose of Mulford's extract in the last part of Fig. 10.

We now come to an injection of 4 c.c. (full strength) of pituitary (infundibular) extract of Burroughs Wellcome & Company. The immediate drop in blood pressure and the perfectly *typical bronchoconstriction* which this injection produces leaves practically no room for doubt, in the light of the recent splendid experimental work of Abel and Kubota, but that this preparation con-

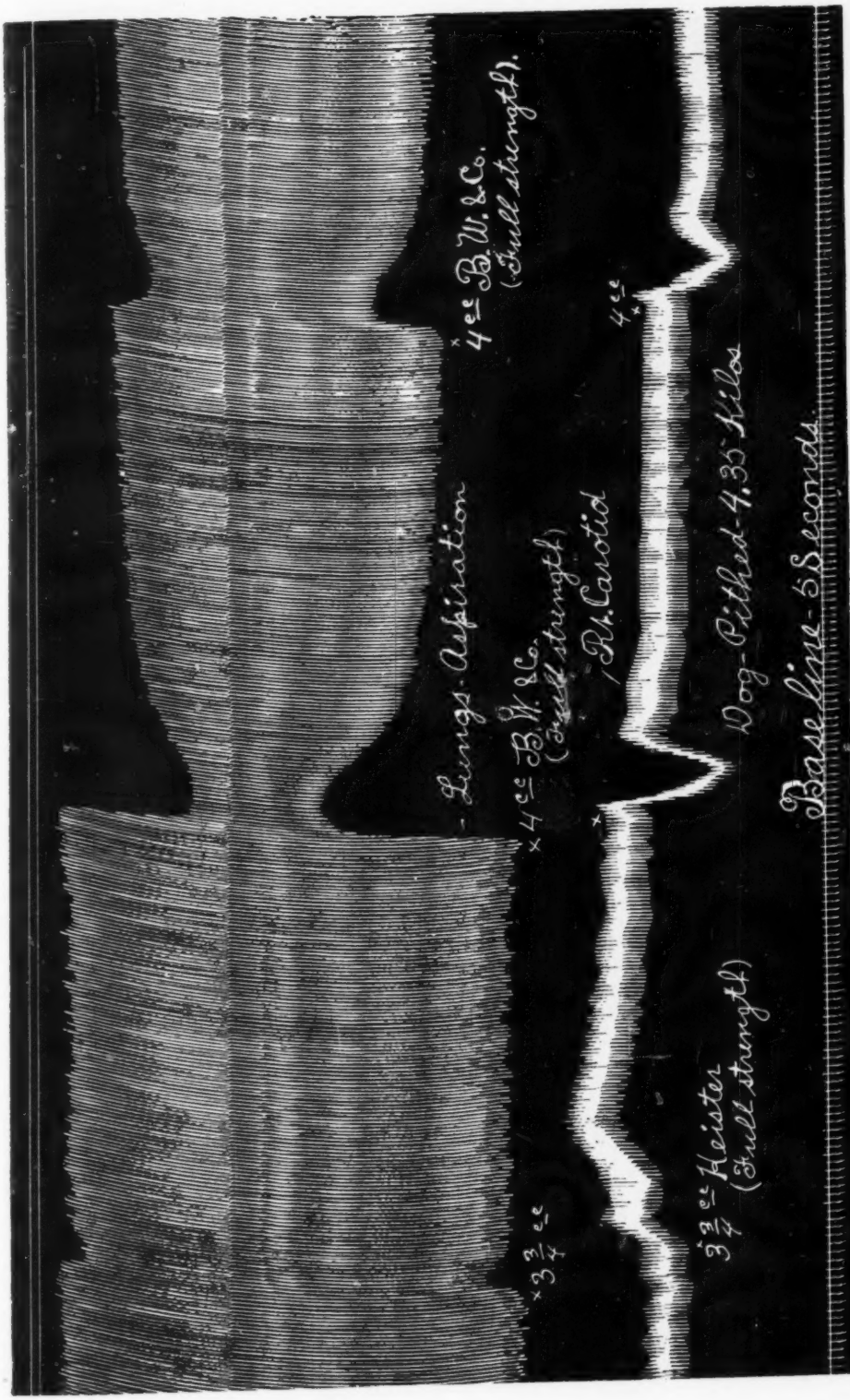

Fig. 11.—For discussion see text.

tained a considerable proportion of histamine ("ergamine"). We should here compare with great care the results of this first injection of 4 c.c. of the B. W. & Co. preparation with that of the 3¾ c.c. of the Heister preparation shown in the first part of the tracing. It seems obvious here that the blood pressure lowering principle must certainly be the same as that which causes the bronchoconstriction and the blood pressure raising principle probably has no action at all on the bronchi. The reader should now compare these results with those shown in Figs. 1, 3, and 4 in which it is shown that a dose of pituitrin which will cause a marked uterine contraction may produce no effect whatever on the bronchioles. But when histamine is injected into the same animal both the uterus and the bronchioles contract. This is a matter of special interest, and we have repeatedly returned to the laboratory to do over again various experiments concerning the results of which we felt that some uncertainty might have arisen. We have worked here with ordinary *commercial preparations,* but these have been the freshest products we could buy, and always stamped by the manufacturer as being active to a much later date than that at which we used them. It may be possible, of course, that a few samples had undergone some deterioration. We do not believe, however, that this had occurred to any material extent. We have considered that point especially in the case shown in Fig. 11. But when we consider that the presence of the substance which caused the great bronchoconstriction would with practical certainty cause a marked uterine contraction, and that the material is sold with its obstetrical use directly in mind, the chances for this substance to have resulted from decomposition in the sealed ampules does seem especially great. It should be particularly emphasized here, however, that 4 c.c. of the full strength extract is an enormous dose for a 4.35 kilo dog. Only a very small amount of histamine need be present in each therapeutic (human) dose in order to make the combined quantities in the four maximum human doses sufficient to produce a very evident effect on the bronchioles which are very sensitive to histamine.

Some commercial preparations contain preservatives, especially chloretone. It was shown by Roth that the presence of this substance did not affect the action of the drug in the tests performed by him. And we feel that in all probability this is true in our experiments also. The very small quantities of chloretone in 3 or 4 c.c. of pituitrin, when injected into a dog of 4 to 12 kilos weight would not be likely to have any detectable results whatever.

Before leaving the discussion of Fig. 11 we should add that later injection of histamine showed that in this animal the bronchioles gave a very obvious contraction when 1/40 of a milligram was injected, but no perceptible contraction was produced by 1/80 of a milligram, so that the limit of the sensitivity of the bronchioles in this case was probably about 1/60 of a milligram. And in this same animal 1/20 of a milligram of histamine mixed with 1 c.c. of pituitary extract sold by Heister gave almost exactly half as big a contraction of the bronchi as did 1/10 of a milligram of histamine alone. That is, the pituitary extract had practically no power whatever toward influencing in any way the normal action of histamine on the bronchi.

We wish now to present briefly some further evidence regarding a possible bronchodilator action of pituitary extracts which might counteract the constrict-

ing action of histamine and thus neutralize its action on the bronchi, while leaving it free to cause uterine contractions. Fig. 12 shows a bronchoconstriction produced by 10 c.c. of histamine solution (½ milligram). Following this there was quickly injected a dose of 2½ c.c. of pituitrin (diluted 1 to 5), i.e., approximately one-half of a therapeutic dose. Time was given for this to reach the lungs, but it failed entirely to dilate them. Consequently a small injection of adrenaline was given to dilate the bronchi a little and thus save the animal from

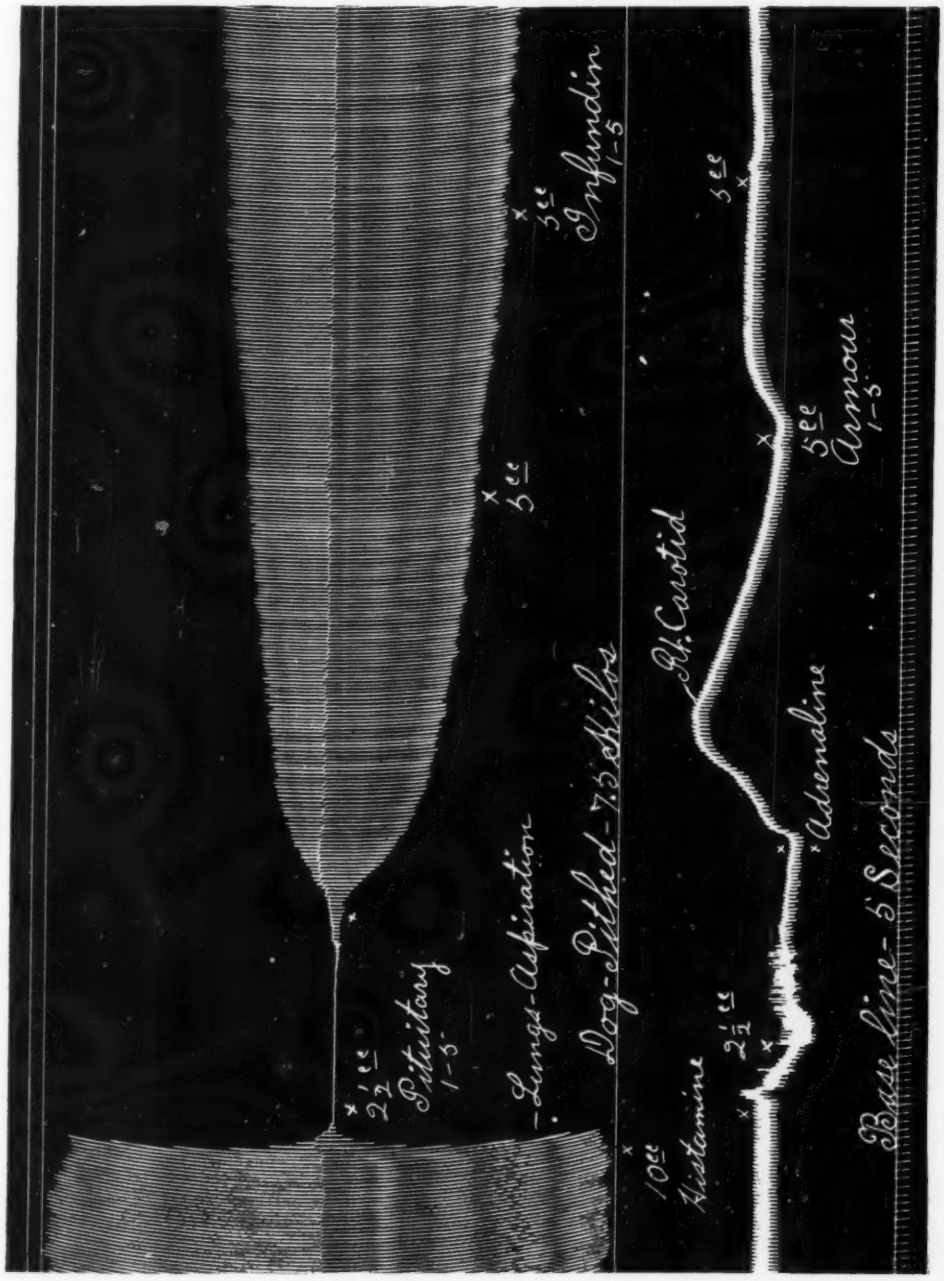

Fig. 12.—For discussion see text.

dying of asphyxia. Following this 5 c.c. of Armour's extract (1 to 5) and 5 c.c. of infundin (1 to 5) were given, but these were wholly without any dilating influence on the bronchi. Practically this same thing is shown again with another animal in Fig. 13.

The matter is approached from a little different angle in Fig. 14. Here 20 milligrams of codeine sulphate were used to produce a bronchoconstriction and two injections of infundin were given in order to determine whether or not the substance would relax the bronchi. Both injections were entirely without effect on the lungs. It should be noted here that these doses of the extract were considerably smaller than the ones used in Figs. 9, 10, and 11, although the doses used in Fig. 14 were fully ample to produce the usually recognized effects of the drug.

We turn now to another phase of the subject, namely, the possibility of making mixtures of histamine and tyramine which would possess approximately the same action as pituitary extracts. This possibility has been suggested by Abel and Kubota, and they quote the patent of A. Hoerlein (U. S. Patent,

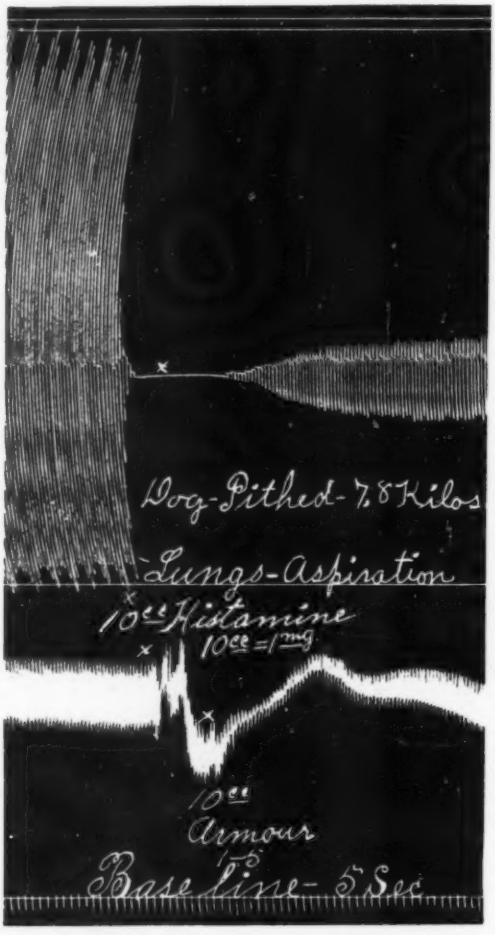

Fig. 13.—For discussion see text.

1,178,720, April 11, 1916) which introduces a combination of parahydroxyphenylethylamine and histamine in the proportions of 1-4 to 30 in aqueous solution as a substitute for ergot.

Figure 15 shows the result of injecting a mixed dose consisting of 7/10 milligram of histamine and 28 milligrams of tyramine, i.e., a mixture of 1 to 40. Obviously no such result as this can be obtained by the injection of ordinary commercial pituitary extracts. We consequently tried a new set of proportions with the results shown in Fig. 16. Here 1 milligram of histamine was mixed with 80 milligrams of tyramine, i.e., a proportion of 1 to 80. Fig. 17 shows the result of injecting ½ milligram of histamine and 50 milligrams of tyramine (i.e., 1 to 100) into another dog. Obviously these results in nowise resemble those produced by pituitary extracts, and we are inclined to suspect that no combination of histamine and tyramine would be likely to produce such action, for if the histamine was in small enough proportion not to affect the bronchi, it would probably be too small in amount to act sufficiently on the uterus. There is an-

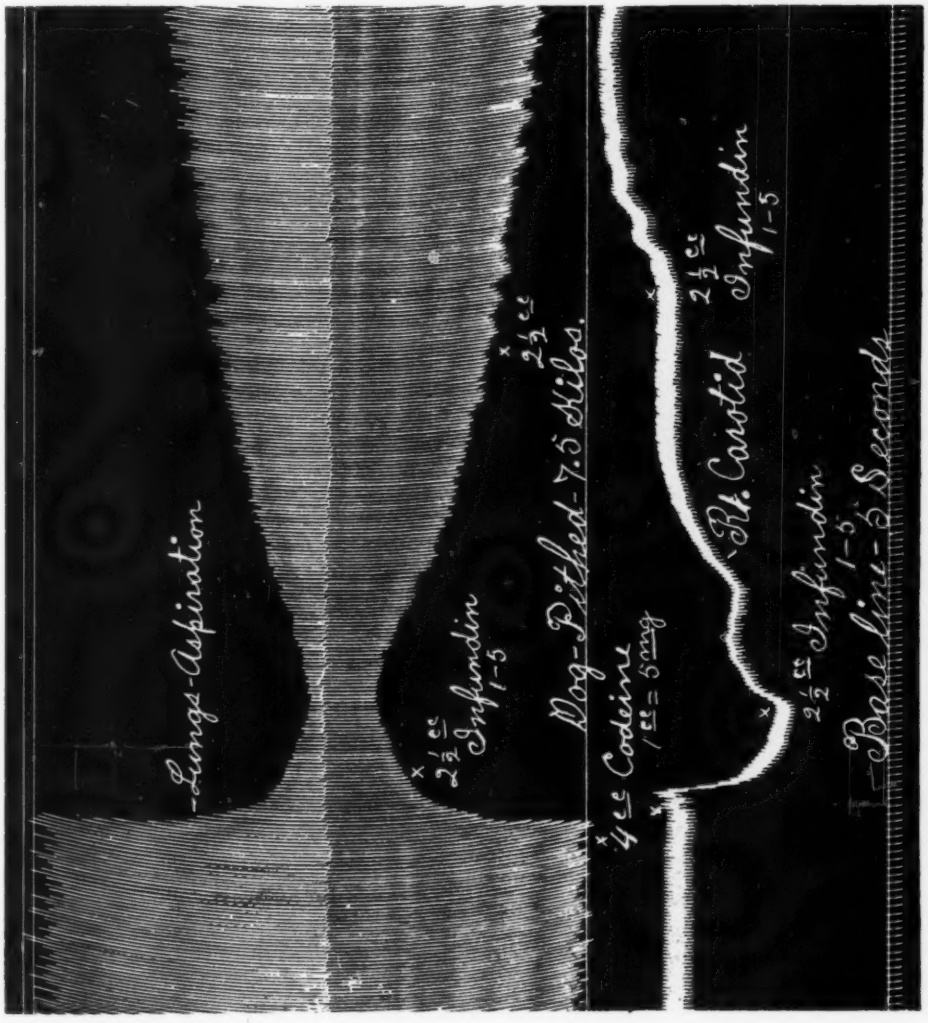

Fig. 14.—For discussion see text.

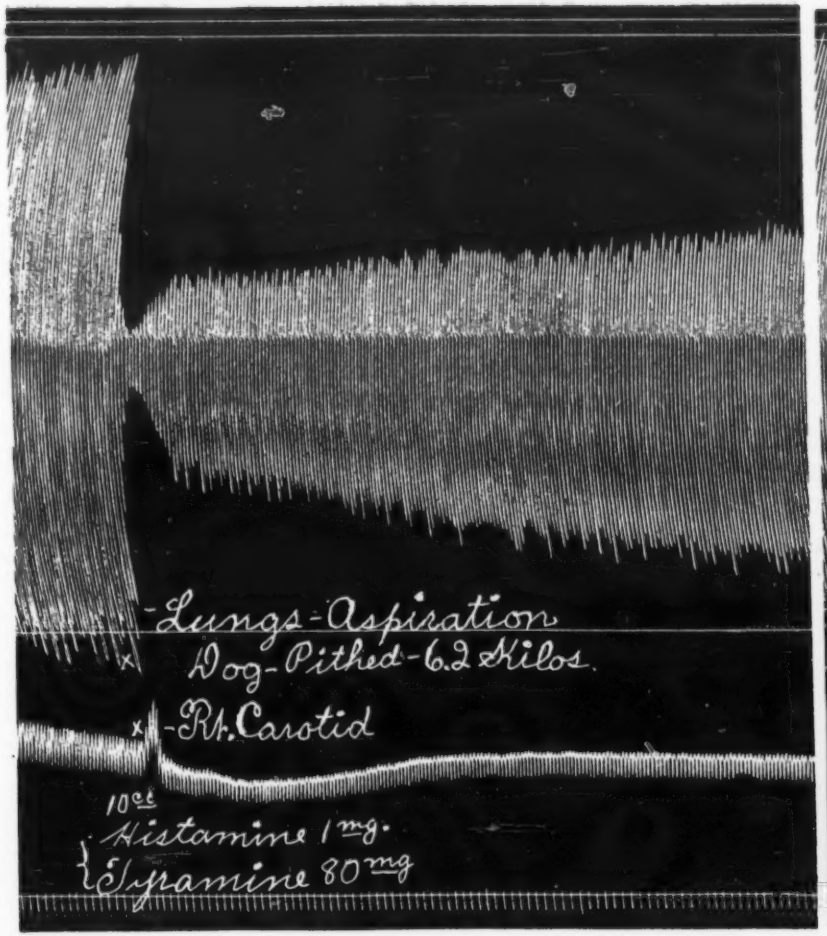

Fig. 16.—For discussion see text.

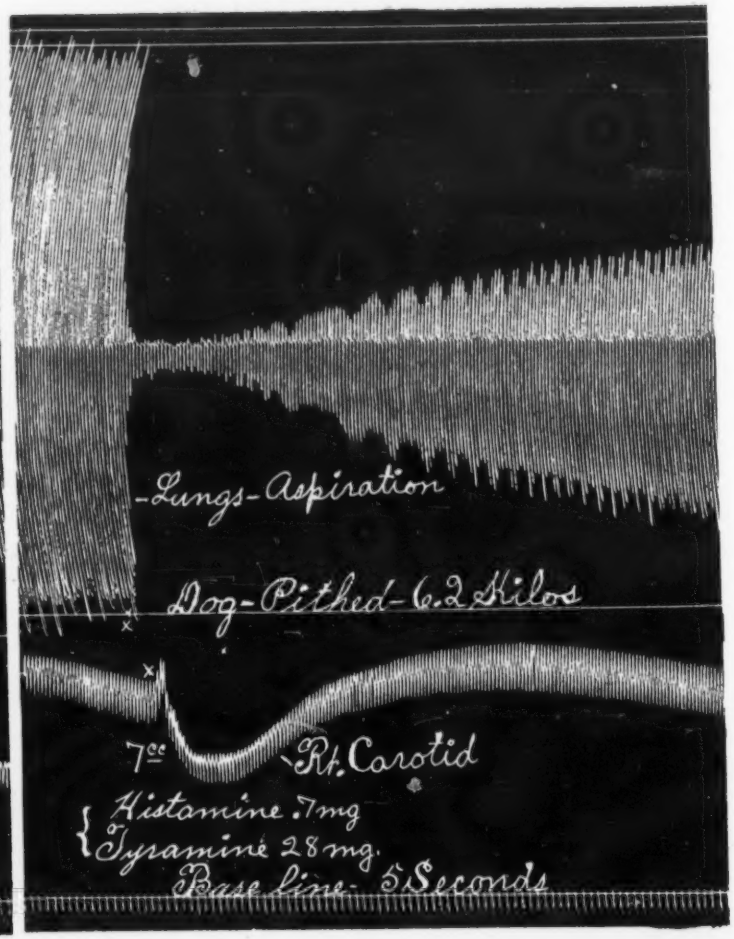

Fig. 15.—For discussion see text.

Fig. 15.—For discussion see text.

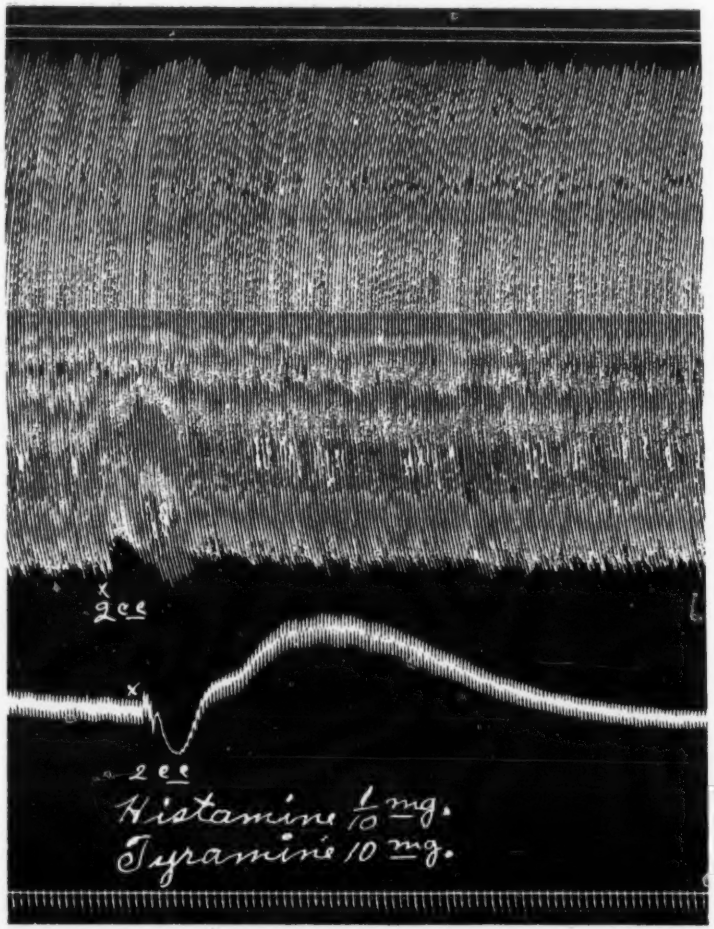

Fig. 18.—For discussion see text.

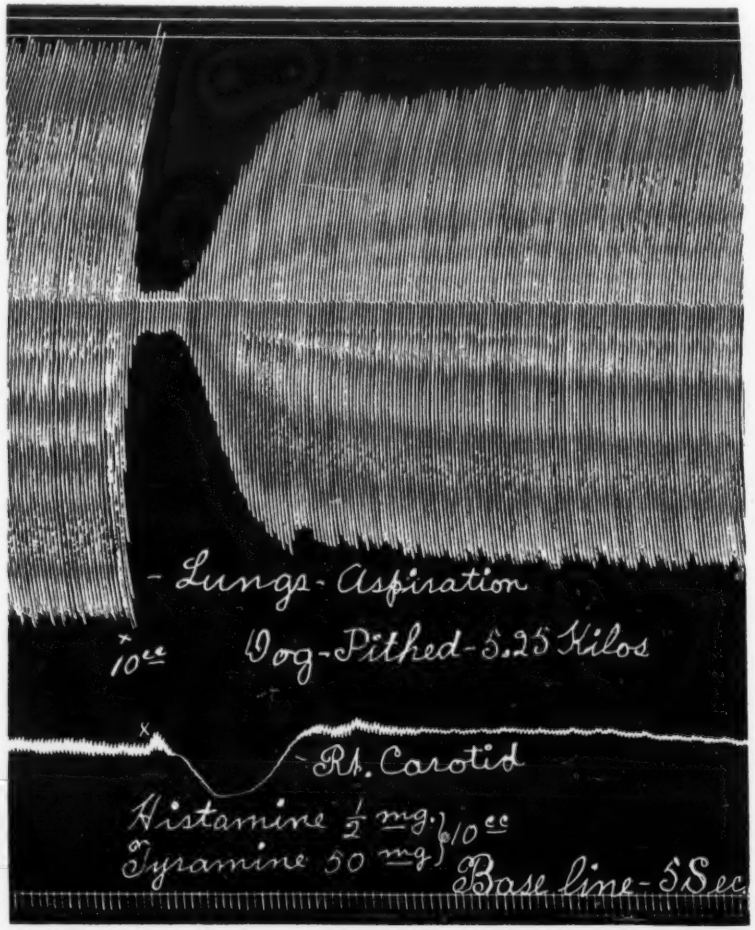

Fig. 17.—For discussion see text.

other objection of possibly more weight than this also to the combination. We have found that when an animal has been injected repeatedly with a mixture of tyramine and histamine so that it has lost its susceptibility to the combination (somewhat after the manner of pituitary extracts) then the injection of pituitary extracts may produce practically the normal type of blood pressure rise. (The reverse of this experiment also holds good.) This test was described long ago by Barger and Dale for various sympatho-mimetic amines. Before leaving this subject, however, we wish to emphasize the fact that we have some evidence indicating that combinations of histamine and tyramine may readily be made which certainly resemble the action of pituitary extracts in many particulars. Fig. 18 is typical in this respect. Here 1/10 of a milligram of histamine and 10 milligrams of tyramine (proportion 1 to 100) produced a rise in blood pressure and a very slight, sharp, transient bronchoconstriction which certainly greatly resembles some pituitary tracings. Without further study one might at once conclude that this combination (1 to 100) was the proper proportion to use in making artificial pituitary extracts. There is, however, one serious objection as will be seen by comparing this tracing with Fig. 17 which was made also from the same animal by a mixture of 1 to 100 histamine and tyramine, but with a dose five times as large. It is seen at once that the increased bronchoconstriction is in almost direct mathematical proportion to the increase in the quantity of histamine injected. Consequently if pituitary extracts consisted of such combinations, then increase in dosage should immediately produce marked increases in the extent of bronchoconstriction. We have shown that that does not occur with some preparations, but does apparently to some slight extent with others.

We may now discuss certain features of the results described in this paper. As it appears to us there are two features which demand special scrutiny. These are the matter of dosage, and the method which we have used to record bronchial contractions. Regarding the first point we may say that we have tried even a much larger range of separate doses and of combinations than we believed to be really necessary. We are sorry that the limit of space prevents us from publishing many other tracings which we have at hand, and which would undoubtedly explain more fully many points which we have barely mentioned herein. There is one point which has especially concerned us. That is the question, is it possible for a combination of histamine and a pressor substance to be made (as a simple mixture) in such proportions that the amount of histamine will be too small to contract the bronchi (which in the dog are exceedingly sensitive to the drug) but will at the same time be sufficient in amount to contract the uterus? The effect of such a combination on the blood pressure and the other smooth musculature we omit from the discussion at present. The only way to obtain evidence on this question is by pharmacologic experiment, and we believe that the results presented above prove that at least some *commercial* pituitary extracts can not be such mixtures. Figs. 1 and 4 probably show completely that the particular extract used in these experiments was not such a mixture of histamine (in appreciable amount) and some pressor substance. While it is possible that some objection might be brought against these experiments, perhaps in regard to the matter of relative dosage, still we have been unable to conceive of any evidence which would demonstrate the matter any more clearly than it is shown

in these two experiments. With reference to certain other commercial pituitary extracts we may say at once that we feel assured that some of these undoubtedly contain histamine, and in all probability in a few preparations the amount is sufficient to be of some therapeutic importance. This histamine we regard rather as an accidental impurity for which ordinary commercial methods are responsible, or else as an added product which is intended to increase the oxytocic action of the product, rather than as a necessary component of all extracts which are efficient in producing contractions of the uterus. In Fig. 1 it is shown that 7/10 of a milligram of histamine produced only a little greater uterine contraction than did the 4 c.c. of (1 to 5) pituitrin. And the histamine here has the advantage of the increase in irritability which the preceding injection of pituitrin produced. Consequently these two doses are fairly comparable so far as their uterine action is concerned. But the action on the bronchi is so wholly at variance that it is practically impossible to reconcile the two results. There can be no doubt but that we are here dealing with two entirely different substances. Histamine is a profound constrictor of the bronchial musculature, but the true active principle of the posterior portion of the pituitary gland is almost, if indeed not entirely, without any action whatever on the bronchial muscles. This holds for the dog. We are unable to say what action pituitary extracts may have on the bronchioles of other animals. But that is immaterial so far as the present point is concerned.

Regarding our method of recording bronchial contractions we may simply say that it is effective in demonstrating the action of exceedingly small doses of histamine, and we have been unable to think of any special reason why it should fail to show a contraction with pituitary extract, if such contraction really occurred.

If the results and conclusions which we have presented above are correct, then it follows as a matter of the greatest probability that the true active principle of the posterior portion of the pituitary gland exerts its action in the body by stimulation of certain nervous elements. This is contrary to the ordinary view which assumes that the drug acts directly on the muscle fibers. It will be recalled by older workers in this field that almost exactly this same history was repeated in the early work on adrenaline. There are now a variety of instances known in which the action of pituitary extracts can be much more plausibly explained on the basis of an action on nerves than of one directly on muscle fibers. Perhaps the most striking of these is the observation by Paton[22] and Watson that pituitrin lowers the blood pressure in birds (duck), and that after repeated injections the fall becomes less and less and may even be finally replaced by a slight rise, i. e., exactly the reverse of the action in mammals. Atropine does not change these results. We may advantageously quote here from Paton and Watson's article (page 419): "The antagonism of pituitrin and barium salts would seem to confirm Dale's contention that the action of the former is upon muscle fibers (it raises blood pressure after ergotoxine) beyond the neuromuscular junction, but on the other hand the way in which adrenaline antagonizes pituitrin (on the blood pressure in the duck), would rather point to the action being upon these terminations." Another example has been noted by Shamoff[23] and also by Hoskins.[24] Shamoff worked with excised loops of rabbit intestine

and found that a variety of pituitary preparations caused relaxation and inhibition. Hoskins did the same thing with intact dogs and got "a clean cut depression of tonus and peristalsis" in five cases out of six. He used commercial "pituitrin," but in three other instances he used saline extracts of old preparations of desiccated gland and got similar results. While we merely mention these few observations, all workers in these fields will readily collect other examples of obscure actions (or lack of actions) on the part of pituitary extracts (such, for example, as its probable failure to produce abortion in the human until very late in pregnancy, and the peculiar and varying reactions of the pupil in different species). And adrenaline itself shows so many striking similarities to the action of pituitrin that a similar pharmacologic basis seems exceedingly probable.

Regarding the nature of nervous structures on which pituitrin might act we can only suggest that possibly some portion of the sympathetic mechanism may be involved, but we suspect that some nervous elements whose course and nature are as yet unknown may be concerned. Pharmacologists are already familiar with such cases, as for instance the action of atropine in checking the marked peristalsis produced by pilocarpine, but failing to prevent vagus stimulation from producing normal peristalsis. (For discussion and references see Cushny, Pharmacology and Therapeutics, 1918, p. 326). And while none of these observations prove that pituitary extracts act on nervous structures to produce smooth muscle contractions, still we believe this view is much more plausible and more in keeping with modern methods of thought than is the older notion of being compelled to assume some peculiar difference in the chemistry of each portion of widely distributed systems of smooth muscle. Even the observation—if it be correct—that histamine itself fails to cause contraction of the rat's uterus is of interest here. And those who are familiar with the widely varying and capricious character of the action of the many sympatho-mimetic amines (Barger and Dale: Journal of Physiology, 1910, 41, p. 19) will be able to appreciate our views on this matter at once.

We feel that the above results probably justify us in suggesting the following conclusions:

1. The true active principle of the posterior portion of the pituitary gland is a simple body of the sympatho-mimetic amine type, which in the dog produces contraction of the uterus but fails to contract the bronchi. With the other smooth musculature we are not especially concerned in this paper.

2. This is in all probability due to an action of the substance on certain nervous elements and not to a direct muscular action.

3. Certain commercial preparations of the pituitary gland apparently contain very small and very variable proportions of histamine, and the amount of this substance is probably great enough in some samples to exert some therapeutic action. But it is in nowise a necessary constituent of first-class preparations of the posterior portion of the pituitary gland.

It is exceedingly probable that the action of histamine on the bronchioles of spinal dogs can be used as a commercial test for the presence of small amounts of this substance in ordinary commercial extracts of the pituitary gland. We presume that excised bronchial rings might be used as a very poor substitute for the method which we have here employed.

5. If the findings reported in this paper are substantiated, then there are very obvious clinical advantages in favor of the pituitary extracts rather than of the very intense broncho-constricting and blood-pressure lowering histamine for obstetrical uses. But in all probability very small amounts of histamine would not be of any serious disadvantage in these preparations.

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REPORT ON EPIDEMIC AND INFECTIOUS DISEASES IN CAMP DEVENS, MASS*

By Paul G. Woolley, M.D., Cincinnati, Ohio

Formerly Major, M.C., U. S. A., Camp Sanitary Inspector and Epidemiologist, Camp Devens, Mass.

THE following preliminary section will serve to indicate the general conditions in Camp Devens and in its environment. The various points are but briefly considered but they will make clear that the diseases which have been observed in the camp personnel were not closely, at least, related to faults of drainage, water supply, sewage disposal, food supply, or insects, and were not apparently related to the geographical location of the camp except as that is related to climate.

Moreover these paragraphs relate especially to cantonment conditions and not to those, inherent or developed, in the extra-cantonment area in which there was much to be desired in the matter of general sanitation.

SECTION I

Camp Devens is situated in Middlesex County, Mass., about 14 miles from Fitchburg, Mass., and about 2 miles from Ayer, Mass., 42 deg. 32 min. North latitude, and 17 deg. 37 min. East of Greenwich. The country is rolling and largely wooded with second growth hard-wood trees. In the camp proper there are occasional clumps of trees and in the open places which are used as drill grounds, the turf has been worn away exposing the underlying sand and gravel. About the camp and especially along the Nashua River, and in the region between the camp and Ayer, there are many marshy places in and about which the undergrowth is vigorous and abundant. In these areas there are many mosquitos which breed in the damp grass and the pools of standing water. Within the camp there is considerable flying dust in dry windy weather, but because of the porous nature of the soil there is but little mud to be carried upon the feet even in very wet weather. The roads are all of tar-bound macadam and so are quite free from dust. In situations where, because of the nature of the roads, the dust would be detrimental, as for instance about the bakeries, the roads and their margins are kept thoroughly oiled.

The camp was designed as a receiving and training camp for New England soldiers. It was planned for the accommodation of a complete division and a depot brigade. In the latter recruits were received, housed, and partially trained, and from it they were later transferred into more permanent organizations, chiefly into units of the 76th Division which from the earliest days of the camp occupied the divisional area. Later, when the 76th Division had gone overseas, men were transferred to the 12th Division which succeeded the 76th at Camp Devens. The 76th Division was, from the start, a replacement division in which partially seasoned and trained men completed training before being transferred to combat divisions. The camp as a whole, then, was devoted to receiving, examining, sort-

*Authority for publication granted by the Surgeon-General's Office, Washington, D. C.

ing, and training, enlisted and drafted troops. After the armistice the camp became a demobilization center and was thereafter devoted to inspection, examination and discharge, of New England troops, and to inspection, examination and transfer of troops belonging in other sections of the country than New England. In its early days the camp was what it planned to be—a New England camp. Later, because of transfers in and out, it became more cosmopolitan.

From the start the camp was overcrowded, sometimes, more, sometimes less, but always some. In certain periods this was general; at other times it was local. It was planned that the area should accommodate approximately 35,000 troops, but this figure was often exceeded. Especially was this true during August and September, 1918. At other times the crowding was due to lack of proper distribution of troops, and was almost constant in the case of the black troops. An early reason for this was that portions of barracks were set aside for recreation rooms—an arrangement which was totally unauthorized, and which was corrected. Also in the early days the Remount Depot and the Public Utilities were badly overcrowded, conditions which were very slowly met by construction of additional buildings. In the Engineer Section overcrowding was noticeable, but was later corrected. The guard houses were generally overcrowded. Even in the early part of January, 1918, there was a deplorable lack of hot water which resulted in lack of use of the bathing facilities.

Despite the overcrowding the health of the whole command did not seem to be very noticeably affected except in the case of measles. The early outbreak of this disease which began in 1917 rapidly exhausted itself and in February had reached a,—what might be called,—fairly normal average. In this period pneumonia was rising, but it was not until the negro troops from Florida entered the camp that it reached anything like epidemic proportions.

The climate is characteristic of New England; i.e., generally and moderately cold in winter with spells of severe cold, and moderately warm in summer with some acutely hot days which are often almost unendurable because of the humidity. The season of 1918-19 was exceptionally mild.

The surface drainage of the camp is naturally good and takes place, as a rule, into the Nashua River or its tributaries. The character of the soil permits of rapid seepage. Originally there were many ponds and pools within the camp area but these have been filled or drained. Those which have not been drained or filled were kept thoroughly oiled, and drip cans for oil were placed at the heads of all streams passing through the camp. The result of all this has been that despite the presence of many mosquitos without the camp area there are very few within it. No anopheles were found within the camp, but in the wooded places along the Nashua River close to the camp specimens have been seen.

On January 1, 1918, the sewage system of the camp was incomplete as regarded the disposal. The collection system was complete, but, lacking a disposal plant, the sewage of the camp was drained directly into the Nashua River, a condition of affairs which added to the size of that already large open sewer. Early in the year the whole system was completed.

Since the completion of the plant the sewage has been disposed of by applying it to sand beds. A main plant of 20 acres receives the sewage of the camp proper, and two smaller plants receive the flow from the Base Hospital. There were pit

latrines located at various places within the camp not convenient to existing sewers and others at the various ranges and at other places used by troops, for instance at Hell Pond,—the authorized swimming place. The sewage flows by gravity to a receiving well the capacity of which is 237,000 gallons. From there it is sent by a centrifugal pump to the twenty sand beds situated on a knoll of sand and gravel above the Nashua River about two miles north of the camp and a few hundred yards north of the corrals of the Remount Depot. The liquid is spread on the beds by wooden flumes. Because the knoll is formed of sand and gravel, no under-drains were provided, the effluent sinking into the soil at the rate of 85,000 gallons per acre. During July, 1918, the flow did not exceed 1,400,000 gallons per day and at that rate of dosage the liquid disappeared so rapidly that the beds were but rarely fully covered. The mat formed on the surfaces of the beds was raked off at intervals of 10 days or two weeks and the beds were then harrowed with a horse drawn harrow. The mat was hauled away and burned. There was but little odor connected with the beds and there were few flies on them. The material taken from the screens at the receiving well is hauled away and buried. It consists largely of rags and paper. The larger of the two Base Hospital plants, about an acre and a half in size, is similar to the main plant but owing to its position the sewage flows into the well from which it is discharged directly by a siphon at the rate of about 72,000 gallons per day. The beds of this plant are underdrained and the effluent flows almost directly into the Nashua River, entering below the surface. Mat forms quickly at this plant and the solid waste is not so thoroughly broken up as at the large plant. The rakings were used for filling low places near the beds and were thoroughly oiled to prevent fly breeding. The second Base Hospital plant, about an acre in extent, receives sewage at the rate of about 24,000 gallons per day, and is underdrained into a creek which flows into the Nashua River.

The garbage of the camp was separated and collected in covered galvanized iron cans, and was sent, daily, to the transfer station where it was delivered to the contractor who removed it. It was presumed that these cans were thoroughly cleansed at the transfer station, but the presumption was erroneous. They were merely cleaned as thoroughly as the water-heating facilities would permit. The result was that flies were more numerous at the transfer station than at any other place in the camp. Manure from the stables and picket lines was hauled away daily and delivered at the railway where it was taken over by the contractor. The stables were kept clean and were not inhabited by any number of flies. There were, however, numerous rats and mice in these buildings.

The water supply of the cantonment is secured from shallow wells on the bank of a small pond just on the east side of the camp. One dug well twenty-eight feet deep and fifty feet in diameter, cased in wooden sheet piling and covered with tar paper covering wood, furnishes the bulk of the supply. During the winter of 1917 the quantity of water from this well was not sufficient for the needs of the camp and so in July, 1918, an auxiliary system of forty driven points, two and one-half inches in diameter and forty feet deep, was completed. These points are spaced thirty feet apart along the bank of the pond near the dug well. The water from the driven points is siphoned into the driven well by exhausting the air in the suction line. The capacity of the system is estimated at from 2,500,-

000 to 3,000,000 gallons per day. The water from the well is pumped against a head of 200-240 pounds into four 100,000 gallon wooden tanks, from which it is distributed to all parts of the camp by gravity. The water was originally pure and the drainage area was practically free from pollution, but occasionally the bacterial counts indicated a leak, probably from the adjacent pond into the well. Therefore the water was consistently dosed with varying small, but sufficient amounts of chloride of lime, or later treated with liquid chlorine. Other sources of water supply were used by troops outside the camp and at the several ranges. The spring and wells from which these waters come were inspected and examined at frequent intervals and posted to indicate whether they might or might not be used for drinking purposes. When the water was of doubtful potability and yet must be used it was treated with hypochlorite in a Lister bag. Bathing facilities were excellent. Showers, hot and cold, were provided in lavatories adjacent to each barrack. In warm weather outdoor bathing was authorized in Hell Pond, a deep lake filled with clear, clean water, situated near the camp.

The milk supply of the camp was, in general, a good one, and if, in certain instances it was not what it should be, the defects were remedied rapidly. The bulk of the milk came from large modern dairies and was packed and delivered under excellent conditions. Twice each week samples of milk were taken from the delivery wagons as they entered the camp and were sent to the laboratory of the Base Hospital for complete examination. The dairies themselves were subject to systematic inspections by the assistant camp veterinarian and were scored. Scores were filed with the dairies, and with the Camp Sanitary Inspector. All milk entering the camp was pasteurized. All meats and vegetables were inspected before they were permitted to enter the camp.

The heating of the buildings was accomplished by means of steam. The system was successful and there was no difficulty in preserving a comfortable warmth even in the coldest weather. Unfortunately this system was not completed until after the onset of the cold weather, in 1917.

The buildings forming the camp were of pine, lined with wall-board. This makes a comfortable house but it becomes most inconvenient in case of infection with cimex.

Kitchens were furnished with hot and cold water and with sinks which drain into grease-traps outside the building. The grease and sediment were collected from the traps frequently enough to keep them in good condition. It was supposed that the original traps were sufficient to care for the grease carried toward the sewers in the waste water from the kitchens. Late in the summer it became evident that unless some change were made, the grease which was being carried past the grease traps would clog the filter-beds, and put them out of commission. Accordingly a new type of trap was authorized and ordered installed. The installation was completed some weeks after the signing of the armistice.

At the main well and at the grenade field on the water shed incinerator latrines were in use, and were completely satisfactory.

The buildings and roadways were well lighted with electricity.

The laundry facilities of the camp were bad in certain particulars until late in the spring of 1919. There was no camp laundry and therefore all articles that

required washing, such as those from the Base Hospital, and those from other sources, were sent to private concerns. It was the rule that these articles were packed in large canvas bags and hauled away by trucks which later returned the washed articles in the unwashed sacks. There was therefore a constant chance of infection and cross infection. In the summer of 1918 however, the bags were discarded at the request of the Camp Sanitary Inspector and were replaced by large baskets which were lined with fresh paper before the clean clothes were placed in them. Still later the camp laundry was put in operation and has been an improvement.

The camp was policed by members of the various organizations and by the Camp Sanitary Squad. The general sanitary condition was kept at a high level, as a rule.

Early in 1918 there was a shortage of warm clothing and as a consequence many men suffered, often severely, from cold. There were many cases of frost bite, epecially of the fingers and ears. Provision was gradually made to remedy this very essential defect. In the meantime there was a very large amount of bronchitis and coryza.

At the time when troops began to return to Camp Devens from overseas the facilities for delousing were absent, though plans were under way, late in the summer, for the construction of a complete delousing plant. Pending the completion of this plant temporary methods were used which served fairly efficiently so far as lice were concerned, but which were exceedingly inefficient so far as clothing was concerned. Much of the clothing handled by the extemporized methods was ruined and could not be reissued.

SECTION II

The following paragraphs relate to problems connected with infectious diseases in the cantonment and are based upon reports made by the Epidemiologist, and by members of the medical staff of the Base Hospital, and upon various miscellaneous reports in the Office of the Camp Surgeon.

Methods of Control.—(a) Measles cases were removed from their organization and sent to the Base Hospital where they were cared for in measles wards. The whole organization was sometimes placed in quarantine for 15 days during which time physical inspections are made at frequent intervals in order that new cases may be caught at an early date. Sometimes only the other members of the same squad were placed in quarantine, and sometimes a whole squad was isolated. The latter method was used to the exclusion of the others during the winter. Recently the squad method has been used with just as good results. Transfers, from one organization to another have been permitted provided that men transferred from an infected unit were sent to an infected unit in their new organization.

(b) Meningitis cases were immediately removed from their organizations and sent to the Base Hospital where they were isolated. Immediately the organization in which the cases belonged were placed in quarantine until the members were cultured. All positive culture cases (carriers) were sent to the Base Hospital. The other members of the organization were kept segregated for a week during which they were treated with chlorazene or dichloramin-T, or a mild disinfectant.

(c) Scarlet fever cases were sent immediately to the Base Hospital. The organization to which the case belonged was quarantined for eight days during which time each member was subjected to careful inspection twice daily.

(d) Diphtheria cases were sent to the Base Hospital. The organization to which the case belonged, or the squad room in which he lived was quarantined and each individual in

the organization or squad room was cultured and "schicked." Carriers were sent to the Base Hospital for treatment. Suggestive "schicks" were given an immunizing dose of antitoxin, and quarantine was raised.

(e) German measles cases were treated in the Base Hospital. No quarantine was kept.

(f) Pneumonia cases were sent to the Base Hospital. Nothing was done in the squads or organizations to which the cases belonged. This seems to be something of an anomaly when such particular pains were taken to prevent the spread of the disease in the wards of the hospitals. Much could be done it seems in the way of prevention of serious complications if the men of an organization or of a command were treated prophylactically in such a manner as to limit the flora of the upper respiratory passages to but one type of organism at most. If the streptococci in the noses and throats of the men could be limited a great gain would be made. The figures which Major Spooner obtained at the Base Hospital are exceedingly suggestive in this connection. He found that practically 100 per cent of the persons examined by him harbored streptococci and that from 5 per cent to 71 per cent of these persons harbored streptococci of the hemolytic type. Lt. Gray and the writer suggested that special care be given to the earliest possible diagnosis of pneumonia, it would be much more to the point to pay especial attention to prophylaxis. With this in view it may be urged that men reporting at sick call with a cough or cold be treated with the object of at least reducing his respiratory flora and if possible of doing away with it. Too often such men are treated by giving them a placebo or a laxative, which is all very well in its place but which does not directly attack the trouble. A man's first sick call is the time to get busy with a possible pneumonia. Men who do not report at sick call and who at the same time have troublesome coughs,—and they are many,—should be sent to the infirmary for treatment. In the absence of such an individual method the only alternative is to treat whole organizations by means of sprays. This can be done and it was done in organizations of more than a thousand men, and done daily at Camp Green with apparently good results. The individual method is preferable.

(g) Incoming recruits were kept segregated for two weeks during which time they were inspected frequently for infectious diseases. Outgoing troops were carefully inspected for signs of infectious diseases and suspicious cases were held. A statement of the condition of the command is sent to the Commanding Officer at their destination.

2. The first infectious diseases (exclusive of venereal diseases) to appear in this camp were pneumonia, measles, mumps, diphtheria, and German measles. There was a single case of typhoid fever and two cases of malaria recognized during October but no other cases of typhoid appeared until the following July, 1918, when the draft brought in two others. Two additional cases of malaria were seen in November and these were the last to be found until the next Spring. From the beginning of the camp there was a gradual, though slow, increase in the incidence of the various infectious diseases through October and November. During this period the men were out of doors during a fair proportion of the time. Later they were more constantly confined to the barracks, or, at least, they chose to occupy their quarters for a larger part of their free time. In the case of measles and German measles the epidemic rise was sharp. In the case of the mumps it was lower. The top of the curve for measles and German measles was reached in January; for mumps, in February. Secondary peaks following the arrival of southern negroes and other recruits appeared in May. The secondary rises were sharper than the primary ones because at this time there was a tremendous amount of overcrowding which acted disastrously upon the sick rate in the blacks especially. Pneumonia on the other hand increased with much greater slowness and reached its maximum in admissions after the measles rise. The pneumonia curve seemed to follow after the curve of upper respiratory infections. Meningitis, diphtheria, scarlet fever, typhoid and paratyphoid fevers, and malaria were at no time epidemic.

Pneumonia seems to have been related not so much to mere opportunity for infection, such as exists in the camp environment, as to previous respiratory affections. Perhaps both factors are essential. Measles, German measles, and mumps appeared, on the other hand, to depend entirely upon multiplied opportunities for infection.

3. Recruiting was most active in October, April, May and June. At various other times in the course of the year small numbers of recruits arrived in camp in numbers of

from 200 to 2000. Following each accession there was an increase in the sick rate from all causes, and in the infectious disease rate, that was roughly proportional to the number of new men. In October the men sent to camp were all becoming accustomed to a completely new life with which few of them had ever had the slightest experience. Cold weather was coming on. The heating plant was not finished. Still conditions were such that they did not have to spend too much time huddled together for warmth. Therefore disease spread slowly. Later as they were more and more confined to their barracks infection spread more rapidly, and this was not confined to the specific diseases but included also the nonspecific infections of the air passages. So we find in December a total of 1013 cases of acute bronchitis, pharyngitis, laryngitis, and tonsillitis treated at the Base Hospital, a number of which indicates an enormous number of other cases treated and untreated in the regimental infirmaries. During December, January, February and March there were more than 3300 such cases treated at the Base Hospital, a figure that is worthy the greatest consideration in studying the pneumonia and empyema situation.

The data relating to the common acute upper respiratory tract infections, are shown in Table I.

TABLE I

	December	January	February	March	Totals
Bronchitis, acute	459	256	182	287	1184
Pharyngitis, ac.	248	196	198	380	1022
Laryngitis, ac.	148	33	11	18	210
Tonsillitis, ac.	158	251	206	290	905
Totals	1013	736	597	975	3321

The figures in the table apply only to cases admitted to hospital. The total for the Camp at large would be far larger. The tonsillitis figures suggest a connection between this infection and the empyema and streptococcus pneumonias.

4. Beside the factor which we call exposure and in which we include general housing conditions, lack of sufficient clothing, as well as direct exposure to weather, stands the factor of fatigue, a rather indefinite one, and one difficult of estimation. In one instance we believe we were able to see that fatigue was definitely associated with an increase in the sick rate. This was in the case of the 303rd Infantry. This regiment was one in which the sick rate had been rarely, if ever, high, and one in which the rate ran at a fairly constant level, without great variation. On May 15th this organization took a practice march to Concord, Mass., an exercise which occupied it until the 18th of May. Previous to May 15th the sick rate had not been above 26.0. The day after the regiment got back from its hike the rate rose and reached 28 on May 20th. On May 21st the rate was 26.6 showing that the increase of sickness was transient though there was still more than a normal amount. The weather was excellent during the whole period. After the 21st of May the sick rate was profoundly modified by additions of new men into the organization so that the further effect of the march can not be seen. It seems that the rise in the sick rate of this regiment on May 20th and 21st was due to fatigue and to exposure which expressed itself in upper respiratory troubles such as coughs and colds and bronchitis. An additional factor to be considered is the dust of the roads, which in this instance was an unimportant one it seems, since, for the most part, the roads over which the men passed were well oiled.

5. The sick rate and rate due to infectious disease was consistently lower among commissioned officers than among enlisted men except in the cases of meningitis and diphtheria. No deaths occurred from infectious diseases among officers except in meningitis which caused one death.

SECTION III

The following paragraphs relate to facts, chiefly statistical ones, associated with the different infectious diseases studied in Camp Devens.

The infectious diseases observed in the Camp were influenza, measles, mumps, pneumonia, meningitis, scarlet fever, diphtheria, German measles, typhoid, ma-

laria, smallpox, chicken-pox and the venereal diseases. Of these influenza, pneumonia, measles, mumps, and German measles were epidemic. Meningitis and scarlet fever showed immature symptoms of becoming epidemic at one time but progressed no further. They and the other diseases were consistently sporadic. Tables II and III are illustrative. In the first, mumps, German measles and venereal diseases are not tabulated.

TABLE II

1918	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Influenza	0	0	0	0	0	0	0	0	14000	664	59	61
Pneumonia	44	52	110	160	89	39	24	112	2595	243	65	71
Measles	252	55	50	18	83	69	56	59	43	126	90	32
Scarlet fever	5	12	13	19	6	2	2	2	1	1	2	4
Diphtheria	0	1	4	5	5	1	4	3	0	0	1	1
Meningitis	1	2	2	3	2	5	1	1	8	18	1	2

TABLE III

1917-1918	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	June	July	Total	Rate 1000
Pneumonia	11	8	16	44	52	110	160	89	39	24	533	22.4
Measles	5	29	168	252	55	50	18	83	69	56	785	31.4
G. Measles	1	8	57	140	30	13	0	0	7	1	257	10.3
Mumps	1	4	8	32	65	62	156	233	160	57	778	31.0
Scarlet fever	0	0	2	5	12	13	19	6	2	2	61	2.4
Diphtheria	1	4	1	0	1	4	5	5	1	4	26	1.04
Meningitis	0	0	0	1	2	2	3	2	5	1	16	0.60
Typhoid	1	0	0	0	0	0	0	0	0	0	1	0.04
Malaria	2	2	0	0	0	0	0	1	1	3	9	0.36
Total	22	55	252	474	217	254	361	419	284	148	2486	99.4

Generally speaking, the health of the Camp was excellent. Taken as a whole the incidence of disease, except during the epidemic of influenza and pneumonia was what may be called normal as compared with other camps and the mortality was low. During the influenza epidemic the death rate compared very favorably with that of other large camps. In certain exceptional instances both incidence and mortality were high, as for example in the cases of pneumonia in southern negro troops. The rule was that all infectious diseases were most frequent in new recruits, especially in those from rural districts, and in overcrowded troops.

Measles was from the start a disease of unseasoned rural troops. The only epidemic of any proportion was that which began in the latter part of 1917, after the weather condition forced men to remain indoors. This epidemic persisted through January and exhausted itself in February, in which month it reached a normal level. With each accession of new troops the number of cases increased. The disease showed relatively fewer complications in this camp than it did in many others.

Measles:

Period, 43 weeks from October 1, 1917, to July 31, 1918	
Average strength of command	30,124
Total cases	785
Annual rate per 1000	31.4
Average non-effective rate per 1000	30.03
(There were no deaths due to measles.)	

Causes of the epidemic:

Infection from civil community.
Susceptibility.
Housing (crowding).
Importation from other camps.
Weather.

With the exception of mumps, measles furnished the largest number of cases of infectious disease during the period under discussion,—in all 785. Taking it by and large the disease was not severe, and, of itself, in uncomplicated cases, it gave rise to no mortality. On the other hand, the complications which followed it were severe, at least in the case of pneumonia, which was frequently followed by empyema. The fact that the largest proportion of complications occurred during January and February appears to mean that the measles was not the immediate cause of the complications but rather the contributing cause, with which was associated the then prevalent respiratory infections, the effects of which were accentuated and rendered more severe by the secondary infection of measles. The records of the camp indicate that the first cases of measles appeared in recent recruits and that later cases were often imported from outside the camp. More recent records (August) showed that the cases of measles which were reported from day to day were, without exception, in recruits, and the daily reports from the U. S. Public Health Service showed cases of measles in most of the surrounding towns. In not a single case observed in this late period was there record that the man had been on leave or pass since coming into the service. All recruits were held in quarantine for two weeks after their arrival. It is therefore evident that all the cases observed in August were men who had been in camp less than two weeks and that the measles was brought into the camp with them. These new men formed foci from which the disease spread to other susceptible persons. Under conditions such as existed during the winter the spread was rapid. In August there was practically no spread. It might be suspected that had the general weather conditions during June and July been similar to those of the preceding winter we should have had a real epidemic. Under these later conditions the complications were fewer and less severe. Therefore it seemed not unreasonable to lighten quarantine in order that as many susceptible men as possible might contract the disease under the best possible conditions. It was believed that such a method of dealing with the disease during the summer months would react favorably upon the amount of sickness and upon the pneumonia incidence and mortality "over there," and also "over here" during the winter. In the absence of permission from the Surgeon General this suggestion was not carried out. Except for pneumonia, the complications of measles were relatively unimportant and resulted in no mortality. Likewise the sequelae were mild. In the last 24 cases there were three pneumonias, all lobular and all mild. It is probable that German measles should be included with measles in discussing the disease because it is one with which the average practitioner is not sufficiently well acquainted to make a certain diagnosis. Even the expert is prone to err, and so it happens that mild cases of measles are called German measles and very frank cases of German measles are called measles. All that seems necessary to be said at this time is that in the cases called German measles at this camp the rate per 1000 was 10.3 for the ten months, that there were no complications of note, and that the days of hospitalization were few.

Pneumonia played a very large part in the morbidity and mortality rates of the camp. In a report from the Base Hospital it was estimated that pneumonia could be held accountable for 45 per cent of all sick days. It has also been esti-

mated that, exclusive of influenza-pneumonia, the mortality rate at this camp was about half that to be expected in a civilian population. The disease attacked both officers and men but was four times as frequent in the men. No empyema complicated the disease in officers. Medical officers suffered more frequently, but no medical officer, nurse, or orderly attending pneumonia cases contracted the disease. Lobar pneumonia was more frequent in negroes, lobular (broncho) pneumonia in white men. The empyemas were predominantly pneumococcic, but the mortality was highest in those due to or complicated by streptococci.

TABLE IV
PNEUMONIA (STATISTICAL TABLE)

Period of 43 weeks from October, 1917, to July 31, 1918.	
Average strength of command	30,124
Total number of cases	533
Annual rate per 1000	21.3
Total deaths	72
Annual rate per 1000	2.8
Case mortality	13 %
Average noneffective rate per 1000	30.03

Pneumonia furnished 21 per cent of the cases of infectious diseases during the above period, and Lt. Gray, in his report on pneumonia and empyema, has estimated that this disease accounted for 45 per cent of all sick days. Also, Lt. Gray suggested that the mortality rate from pneumonia in Camp Devens was about one-half of that to be expected in civilian population under the usual circumstances. This low rate was due to several factors: (a) The excellent general physical condition of the men of the command; (b) The absence of very young and very old persons; (c) the early diagnosis and treatment of sick. The disease attacked both officers and men, but the rate among the men was nearly four times as great as that among the officers. Also there were no cases of empyema and no deaths among officers, a state of affairs determined by (a) the better physical condition of the officers and their previous experiences in other camps, (b) less exposure and less crowding; (c) better attention to ventilation. Medical officers suffered twenty times as often as line officers, but no medical officer, nurse or orderly attending pneumonia cases was attacked by the disease. Organizational incidence of pneumonia can not be interpreted. The Field Artillery had the highest rate, and was followed by Infantry, Depot Brigade, Engineers, and Machine Gun Battalions. There were no cases in the Sanitary Train or the Base Hospital Detachment. Empyema was the one great cause of pneumonia deaths, accounting for 89 per cent of the black mortality and 68 per cent of the white. It appeared in lobar pneumonia, in black men, in but one-third as many cases as in white men, and in one-half as many cases of lobular pneumonia in blacks as in whites. Lt. Gray thinks this was due to the fact that the negroes resisted the pulmonary infection less well than the whites and they therefore did not live long enough to develop complications. It may also be that blacks were not so frequently carriers of streptococci as whites. Among the blacks 94 per cent were of the lobar type; among the whites 74 per cent were lobar. It is an interesting fact that pneumonia has not been, as a rule, a disease of very recent recruits. In Gray's series 14 per cent of the cases appeared in men who had been in the serv-

ice for four months and 10 per cent were in men who had been in the service for two months, figures which indicate that the ground was being prepared for the attack of pulmonary invaders. This has been interpreted to mean that the upper respiratory tract infections (including measles) were essential factors in the whole situation and that exposure to weather, and defects of ventilation were the fundamental controlling, or better, predisposing factors—the ones which account for the tremendous incidence of the so-called coughs and colds,—which, beginning as acute processes, become chronic, and frequently purulent with the passing of time. This conception is borne out, in a way, by the fact that twenty-four of the first hundred cases of pneumonia followed measles, while in the second hundred cases of pneumonia only nine followed measles. The first hundred cases of pneumonia occurred during the period between September 27, 1917, and February 13, 1918, a period during which the weather conditions were at their worst. If measles had been the controlling factor there should have been as many postmeasles pneumonias in the second hundred cases as in the first. Of the 485 cases studied by Gray only forty-one followed measles, and of these thirty-three occurred during the severest part of the winter. Of these forty-one cases thirty-two per cent died. Of 588 cases of measles only about 7 per cent contracted pneumonia. In 44 per cent of the cases of pneumonia, taking Gray's series as a basis for discussion, the organism causing the disease was not determined. In 44 per cent the pneumococcus was found, the streptococcus alone in 9 per cent, and both pneumococcus and streptococcus in 3 per cent. But 49 per cent of the streptococcus cases died, 36 per cent of the mixed cases died, and only 12 per cent of the pneumococcus cases died.

There were seventy-seven cases of empyema, 53 per cent of which were due to streptococcus. Seventeen per cent of the cases showed a mixed infection. The mortality in the pneumococcus group and in the two groups of streptococcus and mixed infection were about equally divided, the pneumococcus having a little the advantage. In judging these cases, however, one must take into consideration the marked lack of resistance of the colored men to the pneumococcus. But even so the great importance of the streptococci must be realized. A special report on pneumonia in white and black men was made in 1918, at which time it was believed that change of climate, exposure and overcrowding were the essential causes of the pneumonia incidence in blacks. At the present time when it is being discovered that a very large number of the southern blacks are subjects of malaria, or hookworm, or both, the feeling grows that these multiple infections may have played an important part in bringing about lack of resistance which has been commented upon. How important syphilis is in this connection can only be surmised. It is interesting to note that the pneumonia mortality was highest during the first three months of the camp. Commencing with October, the percentage figures are as follows: 27, 25, 16, 11, 12, 11, 9, 13, 12—an interesting series which suggests either that treatment improved or that a certain immunity to the prevalent infections was developed.

In April, May, August, and October, the bulk of pneumonia cases occurred among the negroes. In April some 2000 southern negroes were received at the camp and from that time on the pneumonia rate of the camp remained above what it would otherwise have been.

The following statistical tables explain themselves. The data relate only to the months of April and May, 1918, because it is only in these months that the comparison between black men and white can be drawn. The black men arrived in camp on March 31 and the following few days of April and there have been practically no additions to their number until a much later time.

Total Cases (Black and White).

Period of nine weeks from March 31 to May 31, 1918:

Average strength of command for the period	35029
Total number of cases in the period	259
Annual morbidity rate per 1000	42.7
Total number of deaths	29
Annual mortality rate per 1000	4.7
Case mortality	11.2%
Average noneffective rate per 1000	42.1

The comparative data for the complete period covered in this table are as follows:

	White	Black
Average strength for the period	33131	1898
Total cases during the period	94	165
Annual morbidity rate per 1000	13.3	501.3
Total deaths from the period	6	23
Annual mortality rate per 1000	1.1	69.8
Case mortality	6.2%	13.9%

The comparative data for April are as follows:

	White	Black
Average strength for April	29402	1927
Total cases	71	99
Annual morbidity rate per 1000	29.1	623.3
Total deaths	4	16
Annual mortality rate per 1000	1.66	99.8
Case mortality	5.6%	16.1%

The comparative data for May are as follows:

	White	Black
Average strength for May	36861	1870
Total cases	23	66
Annual morbidity rate per 1000	6.9	414.3
Total deaths	2	7
Annual mortality rate per 1000	0.6	44.4
Case mortality	8.7%	10.6%

The meaning of the facts given above in tabular form will be more striking, perhaps, if they are stated in this form: If the morbidity rate for the negroes had existed among the white men of the camp there would have been 2849 cases of pneumonia in this group. If, on the other hand, the white rate had existed among the negroes this group should have had but five cases of pneumonia. These figures are based upon the estimate that 8.6 per cent of the 1898 negroes had pneumonia, as against 0.28 per cent of the 33,131 white men.

When it is found that while the negroes formed 5.4 per cent of the average population of the camp, they furnished 63.7 per cent of the pneumonias, it at once becomes apparent that an explanation of the conditions is needed. A careful going-over of the situation indicated that there were two main factors to be considered. One of these is that which takes into account change of climate, by which we mean to a certain extent exposure, and the other is bad housing conditions; i.e., overcrowding in barracks. Undoubtedly the change of climate and

exposure was the primary factor in leading up to the conditions, but it is just as certain that the element of overcrowding accentuated and tended to make permanent the high morbidity rate among the negroes from Florida. The fact that in some barracks white men were crowded together emphasizes the factor of change of climate and exposure in the blacks. At the same time it is reasonable to suppose that had there been no overcrowding the pneumonia rate would have been lower, not only among the blacks, but also among the whites. In the barracks of the Engineer Battalions the cots were so close together that there was barely room to pass between them, and occupying these cots were men, 75 per cent to 80 per cent of whom (according to the medical officer) had chronic coughs most troublesome at night. Observation indicated that the estimate of the medical officer was reasonably close to the facts.

Influenza and pneumonia in epidemic form caused the most serious condition. It invaded the camp at a period when there was most crowding and came completely unheralded. The result was that in the course of a week or ten days the Base Hospital and the infirmaries were almost overwhelmed. There were too few doctors, nurses and enlisted men of the medical department to meet the emergency and it was only after considerable delay that the personnel deficiency was met. Throughout the hospital and throughout the camp all cots were screened and throughout the days and nights very frequent medical inspections were made. By the time the disease had exhausted itself more than 14,000 cases had occurred, complicated in 2817 instances by pneumonia, and with 787 deaths. The case mortality was approximately 28 per cent. During the influenza epidemic the morbidity and mortality rates were lowest in the 36th Infantry, in the Remount Depot and in the Quartermaster Corps. The reasons for this seemed to lie in the larger proportion of seasoned men in the 36th Infantry, in lack of crowding (Remount and Q. M. C.) to outdoor work (Remount and Q. M. C.), to early screening of the cots (36th Infantry), and to methods of washing mess kits (pooling method—Remount). The Quartermaster Corps and 36th Infantry messes used graniteware dishes which were washed in bulk and not individually.

It is worthy of note that immediately after the order, prohibiting individual washing of mess kits and dishes, went into effect, the incidence of infectious disease as a whole dropped. The effect upon the measles rate seemed especially brilliant.

A complete study of the epidemic has been published in this Journal, 1919, Vol. 14, No. 6.

Meningitis has been relatively uncommon. The only time when it seemed to be taking on epidemic characters was immediately after the influenza epidemic. These cases appeared within a relatively short period in patients in the Base Hospital and in certain organizations in the Depot Brigade. After the personnel of the Base Hospital and of the affected organizations in the camp had been cultured, and the carriers isolated, the total personnel of all organizations was treated with applications of argyrol in nose, throat, and eye. After this no further cases appeared. Several carriers were discovered in the Base Hospital personnel, including two ward surgeons, one nurse, two ward orderlies, and one member of the Medical Detachment.

Following is a statistical table which indicates the extent of meningitis in the camp:

Period of 43 weeks from October 1, 1917, to July 31, 1918	
Average strength of command	30,124
Total number of cases	16
Annual rate per 1000	0.5
Total deaths	6
Annual rate per 1000	0.19
Case mortality	37.5%

The essential factors in the cases, all of which were sporadic, seemed to be those indefinite things included in the term individuality, and overcrowding, which in respect to the last six cases seemed almost dominant.

Mumps:

Period of 43 weeks from October 1, 1917, to July 31, 1918	
Average strength of command	30,124
Total number of cases	788
Rate per 1000	31.5

Mumps was not a serious feature of the disease problem except as it influenced the noneffective rate. The number of cases was fairly large and luckily so when one considers the effect these same cases would have had on the noneffective rate overseas. It seems a wise thing to allow mumps to run its course in a command so long as the facilities for treatment are good. Just what the number of complications has been can not be said until the records are completed, but it has certainly been small. No disability following the disease has been reported.

Scarlet fever:

Period of 43 weeks from October 1, 1917, to July 31, 1918	
Average strength of command	30,124
Total number of cases	61
Annual rate per 1000	2.4

Scarlet fever was not epidemic in this camp and was as a rule a disease only of recent recruits. Of fifty-one tabulated cases 33 per cent were in men of less than two months' service. Very commonly it happened after a period during which there had been no cases in the camp that a new case would be found in a man arrived from another camp, or in one entering the camp from civilian life. The same phenomena were observed at Camp Green during the early months of 1918. The disease was exceedingly mild. It is perhaps this lack of virulence which accounts for the fact that it did not become epidemic. Most of the men may have been at least relatively immune to the disease and so either escaped it entirely or acquired it in such a mild form that they went unnoticed. If this be true then many of the men have acquired an active immunity.

Diphtheria was mild and readily controlled. Its incidence has been consistently low, giving a rate of 1.04 per 1000. One case died. This was a man who came from a western camp to Camp Devens with a detachment with no medical officer. The man was attacked by the disease shortly after entraining, and after two days en route was taken to the Base Hospital, where, in spite of treatment, he died.

Typhoid and paratyphoid did not originate in a single instance within the camp. The three cases which have been reported were all of external and civilian origin, and were admitted to the Base Hospital almost directly from civilian life. Therefore, like malaria, these diseases were imported. With but one exception all of the few cases of malaria were in men from the southern states. The one exception was of eastern Massachusetts origin.

TABLE V
SUMMARY

RATES (ANNUAL ADMISSION) FOR SIX MONTH PERIODS IN 1918		
	Ending June 28	Ending Dec. 27
Pneumonia	25.5	171.9
Influenza	0.0	760.3
Dysentery	0.0	0.05
Malaria	0.1	0.85
Venereal	91.1	75.6
Measles	39.6	24.7
Meningitis	1.0	1.8
Scarlet fever	2.8	0.6
Annual admission rate per 1000 (disease only)	970.7	1715.6
Noneffective rate	39.28	57.5

THE "DELAYED NEGATIVE" WASSERMANN REACTION*

By Guthrie McConnell, M.D., (Cleveland, Ohio) Major, M.C., U.S. Army

IN CARRYING out the Wassermann reaction the usual custom is to employ at least two antigens, one of which is a plain alcoholic extract of tissue, generally beef or human heart. The purposes of such a procedure are several. It must be remembered that the Wassermann method for the detection of syphilis is not a true immunity reaction in that the so-called antigen is not a true antigen. Its activity being in no way dependent upon its being obtained from syphilitic tissues. Consequently methods for the original diagnosis should not be used if they are so delicate that there is a danger of obtaining positive results when the products of the activities of the organism of syphilis are not present. Yet there are instances in which a more delicate reaction is of great value.

For ordinary diagnostic purposes the plain alcoholic antigen is probably the best, it being taken for granted that the condition has never been diagnosed and has never had any antiluetic treatment. Under such conditions a definitely positive reaction can be relied upon. The difficulty, however, lies in the proper interpretation of a negative result with the above-mentioned antigen. Unfortunately the statements of patients, particularly in the army where so much depends upon a disability being "in line of duty," can not always be relied upon. Consequently it becomes a matter of importance to obtain as accurate information as is possible.

In the Laboratory, Base Hospital, Camp Devens, Mass., since the middle of February two antigens have been employed: one a plain alcoholic, the other cholesterinized extract. As is well known the latter is a much more sensitive antigen, in fact so much so that it is rather unwise to make a positive diagnosis based on it alone. It has been recognized that this antigen if it gives any reaction at all, commonly gives a well-marked one. Its chief value, therefore, lies in the information that it gives concerning the effect of treatment upon the disease. By its means we can follow quite closely the results that are being obtained, determine when the treatment may be discontinued temporarily, and also when the case may be considered cured. It may, also, be of value when carefully correlated with the case history and clinical findings in picking up individuals who have been concealing important data. In relation to this matter come those reactions which for convenience sake may be referred to as "delayed negatives."

In performing the Wassermann reaction the textbooks, with but very few exceptions, state that after adding the hemolytic system, the tubes should be thoroughly shaken and then placed in the water-bath or incubator for from one to two hours; the general impression obtained being that the tubes are not to be disturbed until it is time for them to be examined finally. In the Medical War Manual No. 6, the directions state that the tubes should be shaken every fifteen minutes, but no reasons are given for so doing other than hastening hemolysis.

*From the Laboratory of the Base Hospital, Camp Devens, Mass.
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Several years ago in the course of routine Wassermann examinations it was noted that every now and then there would be a specimen of blood that up to a half hour after having had the hemolytic system added and being placed in the incubator would remain as a strongly positive reaction. Very shortly after that time the blood would very quickly hemolyze and well before an hour had passed would show no traces of unhemolyzed cells. In the few cases observed at that time it was found that although no clear evidence of syphilitic infection could be obtained, yet there was a history of syphilis or a positive Wassermann in some other member of the family. These cases were picked up on account of the habit of shaking the tubes every fifteen minutes. About this same time G. M. Olson published a brief article (*Journal of Laboratory and Clinical Medicine*, 1916, i, *p.* 704) entitled "The 'Delayed Negative' Wassermann Reaction" in which he called attention to the same phenomenon. He commented on its importance from the diagnostic point of view in cases of suspected primary sores, and also in the tertiary stage when so many patients give negative reactions. No reference, however, is made in regard to the frequency of the "delayed negative" reaction.

Since February 5, 1919, a close watch has been maintained on all Wassermanns to determine, if possible, the significance of these delayed negatives, as well as the frequency of their occurrence. During the months of February, March, and April, 1793 Wassermann tests were made and of that number there were 18 that were considered delayed negatives. In every case cholesterinized and plain alcoholic antigens were used. A sheep cell hemolytic system was employed and the tubes placed in a water-bath at a temperature of 37° C. after having been well shaken. After this they were examined every fifteen minutes. In this report by delayed negative is understood one in which the tube containing the cholesterinized antigen showed no hemolysis at the end of thirty minutes but had completely cleared by the time of the following examination fifteen minutes later. In none of these cases was there any such delay in the tube containing the plain alcoholic antigen. In them, hemolysis was complete before the half hour period terminated. If no other antigen than the alcoholic had been used, or if the tubes had not been examined until they had been in the water-bath for an hour the report would have gone in as a negative Wassermann.

The difficult part in these instances is the proper interpretation of the findings. Are they to be reported as negative or positive, or shall they be reported as negative with the alcoholic, and positive with the cholesterinized antigen, and the attending physician allowed to draw his own conclusions? As a rule the majority of consultants will wish a definite expression of opinion from the laboratory as to the significance of such results.

In the hope of coming to some definite conclusion the above mentioned 18 delayed negatives have been studied as carefully as possible. It has been found that they can be placed in one of three classes. First, those that give a frank history of syphilis, either of long standing and little or no treatment, or of more recent infection with treatment. Second, those that might be considered as questionable on account of their generally loose sexual relations. Third, those in whom there can be obtained no history of venereal infection, and who give no clinical symptoms. In the actual number of cases the classes come in the order mentioned.

Of the eight in class one giving a positive history of luetic infection, seven of them have had antisyphilitic treatment, varying from one injection of some arsenic compound to a prolonged course of neosalvarsan and mercury. The eighth case had syphilis eight years ago, but no information relative to treatment was obtainable.

In Class II, the six questionable cases, all denied having had syphilis, but each man had or had had gonorrhea. Of these, three were colored men and their statements are distinctly unreliable. If any of them have had a sore on the penis it is nearly always referred to as a "hair cut," and the diagnosis is rendered more difficult by the fact that the skin lesions are frequently so inconspicuous as to be easily overlooked by the patient. Two other cases were admitted and under treatment for gonorrhea. The sixth man had had gonorrhea ten months previously, but at the time of entering the hospital he had no symptoms of any venereal infection. He was admitted as a case of acute bronchitis.

In Class III are four cases in which delayed negative reactions were obtained, but in which no history of luetic infection was obtainable. One of these was a man who was a chronic alcoholic and who had been admitted to the hospital for bronchitis and alcoholism. Knowing the inhibiting action of alcohol it might be that a strongly positive reaction would have appeared after the effects of the alcohol had passed off. A second case, who denied infection, had been in the ward for a week suffering from acute cholangitis. Of the other two, one had been admitted for lobar pneumonia and one for influenza.

As a matter of checking up the results of treatment it would appear that the delayed negative is a matter of some importance. By examining the tubes every fifteen minutes such reactions will be noted and a better record kept of the condition of the patient. In this way a case that is still in need of treatment will not be overlooked. Seven of the positive cases first mentioned give in each instance a distinct history of infection with subsequent treatment, which although evidently beneficial was not sufficient to eradicate the disease.

In the second group of six cases one feels almost justified in considering the three colored men as positive cases, their statements to the contrary notwithstanding. Their ages were twenty-four, twenty-five, and twenty-six and there is no question as to their having been exposed frequently, particularly as each had had gonorrhea, one of them claiming that he had had it for ten years. The remaining three had had gonorrhea and there is no question as to frequent exposures.

Of the four in group three it is difficult to come to any definite conclusions. They are all considerably older than the average of the other groups, each man being 29 or over, old enough and experienced enough to realize the disadvantages of telling too much about themselves. One of them had been admitted to the hospital for acute alcoholism, but in the others there was nothing found in the history that would tend to incriminate them. Consequently they must be given the benefit of the doubt and be considered as negative cases.

In regard to the frequency of delayed negatives, 1 per cent of all Wassermanns is what is indicated by these figures. Of the total number, approximately 0.44 per cent give a definite history of syphilitic infection, 0.33 per cent were probably syphilitic, leaving 0.23 per cent as probably negative.

To briefly summarize it would seem advisable that readings should be taken every fifteen minutes after the hemolytic system has been added and the tubes placed in the incubator or water-bath. By so doing there will be a certain number, about 1 per cent, that will give a so-called "delayed negative" reading. Of these nearly three-fourths will give either a positive or a very suspicious history in regard to venereal infection. Although such reactions are few and far between, very little additional labor is required, and information about the occasional case is frequently important.

CLASS I—POSITIVE CASES

H. F., 26, Colored, Florida.	Syphilis 8 years ago, gonorrhea 4 months ago. Feces negative, malaria negative. Admitted for follicular tonsillitis.
J. R., 26, Colored Florida.	Chancre 1910. Gonorrhea August, 1918. Undergoing treatment with arsenobenzol.
B. R., 28, White, Italy.	Infected January 1918. Received 8 injections of neosalvarsan from July to November, 1918, also 9 injections of mercury.
A. G., 27, Colored, Georgia.	Syphilis and gonorrhea 4 years ago. States that he had had one injection by way of treament.
S. S., 21, Colored, Iowa.	Denies syphilitic infection but admits that he has had three injections of "606."
A. L., 29, White, Italy.	Chancre 10 years ago. Chronic gonorrhea at present, also pulmonary tuberculosis. Has been given "606" and mercury.
C. B., ?, White, ?	General paresis. Positive Wassermann with spinal fluid. Amount of treatment unknown.
L. C., 26, White, Penna.	Had sore on lower lip during Aug. and Sept., 1918. Urethral discharge Sept.-Nov., 1915. Had eight salvarsan treatments in France in June, 1917, and Dec., 1918.

CLASS II—SUSPICIOUS CASES

J. McP., 22, Colored, Florida.	Denies syphilitic infection. Has had gonorrhea twice. Feces negative. Malaria negative. Admitted for influenza and bronchopneumonia.
E. C., 25, Colored, Indiana.	Gonorrhea 8 years ago. No luetic history.
N. J. G., 24, Colored, Florida.	Gonorrhea 1909. Says that it lasted ten years. No luetic history. Admitted for bronchopneumonia.
C. B., 25, White.	Gonorrhea 18 months ago, and acute attack at present.
J. P., 24, White, Macedonia.	Gonorrhea ten months ago. No history of lues. Admitted for acute bronchitis.
F. P., 25, White, Kentucky.	Gonorrhea for past month. No luetic history.

CLASS III—NEGATIVE CASES

M. M., 31, White, Ohio.	Denies all venereal infection. Admitted for bronchitis and alcoholism.
R. F., 31, White, Michigan.	Denies all venereal infection. Admitted for influenza.
F. T. D., 29, White, Arkansas.	No venereal history. Admitted for lobar pneumonia.
L. E. D., 31, White, Canada.	No venereal history. Admitted for acute cholangitis. Also has a Trichuris trichiura infection.

FURTHER OBSERVATIONS ON THE RELATION OF AORTIC INSUFFICIENCY TO THE WASSERMANN TEST*

By Julien E. Benjamin, Capt. M. C., (Cincinnati, Ohio), and Sydney J. Havre, 1st Lieut. M. C., (Akron, Ohio), Camp Funston, Kansas

IT IS noteworthy that the cause of insufficiency of the aortic valves in young adults, uncomplicated by any other valvular lesion, is attributed to a syphilitic infection in the large majority of cases. According to the following authors the incidence is expressed as follows:

Longcope,[1] in summing up the situation, says that 75 to 80 per cent of all aortic insufficiencies give positive evidence of syphilis, and also that signs of aortic insufficiency unassociated with any other valvular lesion in an individual under fifty are practically pathognomonic of syphilis.

Collins and Sachs[2] found 84 per cent of all cases of this disease due to syphilis.

Citron,[3] in fortifying his work by the Wassermann test, found a positive reaction in 60 per cent of his cases.

Cabot[4] has recently stated that he believes it possible for a primary rheumatic aortic insufficiency to occur with the preservation of the integrity of the mitral valve, but that such an event is a rare one.

From these figures, it is very evident that the most careful observers find a very close relationship between these two phenomena; syphilis and uncomplicated aortic regurgitation. The results which are reported in this paper fail to bear out the observations noted above, for a positive Wassermann reaction was obtained only in 11 per cent of the thirty-three cases referred for the test. Major Broman, who supervised the reactions at the Base Hospital at Fort Riley, Kansas, states that the element of error is no more than is to be usually expected. Further, the positive and doubtful reactions occurred in those subjects who gave an undoubted history of syphilis in its various manifestations. In the remaining number there was absolutely no knowledge of an existing cardiac condition, and it was only by close questioning that a history of predisposing infection could be obtained. From the appended tabulations, it will be seen in how many cases a definite history was related. It was because the histories coincided so closely to the laboratory findings that a report of this kind was considered justifiable.

The observations were conducted in each instance on recruits during their entrance examinations. The venipunctures were made by one of the cardiac examiners at the time of the examinations so that no unnecessary time was lost in rejecting the individual. The usual cardiovascular history was taken in each case.

Thus in Table I there are recorded 19 cases which give undisputed histories of rheumatism; 2 with doubtful histories, as against 3 cases in which reliable histories of lues were obtained, and one doubtful. In all 4 cases with positive histories of syphilis, the Wassermann reaction coincided. These cases of pure aor-

*Authority to publish granted by the Surgeon-General's Office, Washington, D. C.

tic insufficiency were found in the course of examination of 44,018 recruits over a period of three months.

TABLE I

TABULATIONS OF CASE HISTORIES AND WASSERMANN REACTIONS

CASE	NAME	AGE	PREDISPOSING HISTORY	OCCUPATION	REACTION (WASSERMANN)
1.	C.B.	21	Rheumatism for six months at 13 Frequent attacks of tonsillitis	Farmer.	Neg.
2.	J.W.K.	21	Frequent attacks of tonsillitis.	Farmer.	Neg.
3.	F.F.M.	21	Rheumatism six weeks at 20. Frequent attacks of tonsillitis.	Farmer.	Neg.
4.	J.R.S.	25	Rheumatism at 13. All of diseases of childhood.	Farmer.	Neg.
5.	P.R.	26	History absolutely negative	Farmer.	Neg.
6.	C.N.B.	21	Rheumatism at 15. Frequent tonsillitis, pneumonia at 13.	Rancher.	Neg.
7.	G.R.	26	Typhoid and pneumonia at 18. Indefinite rheumatic history 10 years.	Farmer.	Neg.
8.	E.N.B.	27	History absolutely negative.	Farmer.	Neg.
9.	O.J.	25	Pneumonia at 17 and 18. Rheumatism 3 months at 23.	Cook.	Neg.
10.	A.E.F.	27	Rheumatism at 19. Frequent tonsillitis diseases of childhood.	Laborer.	Neg.
11.	C.T.C.	30	Rheumatism for past six years.	Laborer.	Neg.
12.	O.T.H.	22	Typhoid fever at 8. Diphtheria at 18.	Clerk.	Neg.
13.	W.W.	21	Rheumatism (?) Syphilis at 18.	Farmer.	Pos.
14.	H.G.F.	22	Rheumatism for 8 years.	Farmer.	Neg.
15.	G.S.	25	Rheumatism 4 years. Frequent tonsillitis. Pneumonia at 23.	Laborer.	Neg.
16.	J.R.	24	Tonsillitis frequent. Syphilis at 17.	Farmer.	Pos.
17.	V.D.S.	31	Diphtheria as child. Malaria at 24. Chancroid (?) 1910.	Laborer.	Neg.
18.	A.H.H.	29	Rheumatism at 27 and 29. Measles at 27 years.	Farmer.	Neg.
19.	A.A.T.	24	Rheumatism at 22 for five weeks.	Steam-fitter	Neg.
20.	H.J.E.	24	Rheumatism at 14 for 4 months. Measles at 20.	Farmer.	Neg.
21.	V.L.E.	22	Rheumatism at 16 for 8 weeks	Farmer.	Neg. (pos.)
22.	E.H.B.	23	Rheumatism at 10, 11, 12, and 13 yrs. Measles at 13.	Farmer.	Neg.
23.	R.N.B.	24	History absolutely negative.	Cook.	Neg.
24.	R.P.	22	Rheumatism at 17. Frequent tonsillitis.	Driver.	Neg.
25.	R.E.R.	28	Frequent tonsillitis.	Laborer.	Neg.
26.	A.C.S.	29	Rheumatism at 23 and 27.	Carpenter.	Neg.
27.	N.P.	24	Rheumatism at 21 and 24. Measles at 22.	Farmer.	Neg.
28.	S.C.S.	25	Syphilis at 23.	Teamster.	Pos. Pos.
29.	A.A.W.	30	Indefinite history of rheumatism.	Farmer.	Neg.
30.	V.T.	31	Rheumatism at 27.	Porter.	Neg.
31.	C.E.G.	25	Syphilis ?	Farmer.	Neg. Pos.
32.	W.B.	22	Rheumatism at 14.	Farmer.	Neg.
33.	F.T.	24	Tonsillitis and measles at 23.	Farmer.	Neg.

TABLE II

THE RELATION OF AORTIC INSUFFICIENCY TO OTHER VALVULAR LESIONS IN 44,018 CASES

1. Total number cases examined	44,018	
2. Total number cases of valvular disease	147	.33% of 1
3. Total number cases of Aortic Insufficiency (Pure)	33	22. % of 2
4. Total number of Aortic Insufficiencies with other lesions	51	34. % of 2

TABLE III

GENERAL TABULATIONS OF RESULTS

In 33 cases of aortic insufficiency.		
Wassermann reaction, positive	4	11%
Positive history of rheumatism	19	57%
Occupations.		
Farmers	19.	58%
Laborers	5.	15%
Cooks	2.	6%
Miscellaneous		21%
Age.		
Average		24 years
Youngest		21 years
Oldest		31 years
Race Of 44,018 recruits examined,		
Colored		14,009
White		30,009
Of these, aortic insufficiency occurred as sole lesion in,		
White	28	84%
Colored	5	16%

CONCLUSIONS

A report is hereby made of 33 cases of aortic insufficiency unassociated with any other organic cardiac disease from a clinical standpoint.

Wassermann reactions, taken in each case, were positive in only 11 per cent as against the reported higher rates of other writers.

Undisputed histories of rheumatism were obtained in 57 per cent of cases. Questionable histories of rheumatism and histories of frequent attacks of tonsillitis were noted in 15 per cent.

A tabulation of results as regards occupation, age, race, and incidence is reported.

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A REVIEW OF THE RECENT LITERATURE BEARING ON THE FUNCTION OF THE THYMUS GLAND

By W. E. Blatz, M.A., Toronto, Canada

THE study of the glands of internal secretion has occupied much attention in the past decade and many theories have been offered concerning their functions.

Of all of these glands, probably the thymus is the least understood, and this brief review of the most important work is offered in the hope that it may prove useful to those who are unfamiliar with the original papers in which it appears.

This work has been concerned with the anatomy of the gland, with the physiologic effects produced by extirpation, and by feeding with the gland substance, and with clinical observations, including the effects of x-ray.

Some uncertainty prevails as to whether the thymus is an epithelial or a lymphoid gland in so far as its activities are concerned. Wallin claims that the branchial epithelium of the lamprey has the *general* property of forming lymphocytes, which would explain the presence of the small thymic cells. Fulci maintains that "the small round cells of the thymus (the lymphocyte-like cells) are elements of epithelial nature, which following successive modifications evolve from the epithelial cells. * * * they are not capable of differentiating into eosinophiles or plasma or mast cells." On the other hand Bell maintains that the Hassal's corpuscles are connective tissue cells. Hammar explains the presence of the small thymic cells by an infiltration of leucocytes which have ultimately gone through a physiologic involution to their present form. Maximaw demonstrated the lymphatic nature of the thymic cells in amphibians and selachiens. Pappenheimer in a series of sera experiments developed small thymic cells from lymphocytes. Douchakeff showed that "granulocytoblasts" were developed only from lymphoid elements and that thymic cells were formed therefrom.

It is known that the thymus gland undergoes a normal involution, but it is remarkable how little the various authors agree as to the extent or time of this process. Baum in dogs gives the ratio between thymus and body-weight as follows: newborn 1:125; two weeks 1:170; two months 1:1600; two to three years present. According to these figures involution begins immediately after birth. Basch gives the above ratio as 1:300 in 3 to 4 weeks and Tongu gives 1:189 in the first to second week. Klose and Vogt say that involution begins in the fourth week. On the other hand Tongu says that gross and microscopic involution does not begin until the fourth month and Hammar claims that it does not begin until the second year. Matti considers involution to begin when the period of most active growth occurs. Hoskins from a compilation of human statistics states that "Although the thymus reaches its greatest absolute size at about the time of puberty, nevertheless relatively * * * it is seven times as large at birth as at puberty" also that "in the growth of the thymus after birth the connective tissues make up an increasing amount of the entire organ." Quoting again from

Hoskins, "Anatomists make an allowance of from 100 to 700 per cent in the normal weight of the thymus at different ages." Can there be any greater confusion than in the consideration of the above figures? One should moreover not overlook the significance of the frequent persistent thymus.

Before considering the literature bearing on the results of extirpation of the gland, there are certain points which should be kept forcibly in mind. The operation is necessarily severe and it is difficult to dissociate the immediate results of shock, etc., from the physiologic effects of loss of thymus influence. The mere fact that the organ does normally involute makes the time of operation of utmost importance. The presence of accessory thymus bodies predicates a serious complication when interpreting results. Only experiments which include a sufficient number of "successful" operations with proper controls should be considered. As before, we shall discuss first one view and then the opposite.

Basch with dogs two days old and controls from the same litter demonstrated a change in the skeletal state at the end of the third week after operation. The bones were softer and more pliable. There was a delayed growth and indications of diminished intelligence. Klose and Vogt found the greatest effect when the extirpation was performed on the tenth day after birth. He divides his results into three periods: a latent period of two to four weeks; an adipose stage of two to three months; a cachectic period of three to fourteen months. Matti corroborates this. Schimizu by injecting a serum, specifically cytolytic for thymus, has succeeded in causing early involution of the thymus accompanied by "all the symptoms commonly attributed to thymectomy." Weymersch records an increased leucocyte count and growth increase after atrophy of the thymus. Gilliberti attributes general symptoms such as collapse to thymectomy.

All observers do not, however, agree that thymectomy has such different effects. In contradistinction to the above the following results are significant. Fischl did not observe any effects of thymectomy with dogs, goats or rabbits. Hart and Nordmann, who operated on the fourth week also obtained negative results. Renton and Robertson performed extirpation experiments on puppies at different ages and found that rickets developed as quickly in controls as in the operated animals. (The controls were puppies of the same litter operated similarly to the *bona fide* operated animals, but without extirpation of the thymus). Renton observed no apparent symptoms in guinea pigs after thymectomy. Park discusses the presence of accessory thymus bodies at great length and made as complete an extirpation as possible and found no change from controls (as above) in procreative abilities, growth or condition of endocrine glands, no rachitic changes. Allen showed complete sexual differentiation in thymectomized tadpoles.

Probably the most complete work on thymectomy has been done by Tongu with a large number of dogs of various breeds and ages, with admirable controls and careful tests extending over a number of years. The following table is worth considering (no doubtful cases were included). Clinical and laboratory tests after operation showed:

I. Body weight—no influence after thymectomy.
II. Growth—no effect—Klose and Vogt 3 stages not shown.
III. Nervous, psychic—no effect.

IV. Blood corpuscles—no effect—number or differential.
V. Change in opsonic index—no change inexplicable by operation results.
VI. Blood pressure—results conflicting.
VII. Histologic—no change—sometimes found thymus accesssory bodies, but they did not seem to affect the result.
VIII. Skeletal system—no change in length, structure, calcium content, callus formation after fracture, etc.
IX. Changes in other organs—none.

Thus we see that there is slight preponderance of evidence indicating that thymectomy is not followed by any definite physiologic effects.

Many experiments have been performed on the influence of feeding thymus gland extract either to normal animals or to patients. We are concerned here rather with the physiologic than the clinical aspect, which will be dealt with later.

Gudernatsch fed thymus extract to tadpoles and produced an increase in size (growth), but a delay in development (metamorphosis). Uhlenhuth on feeding thymus extract to young salamanders observed tetanic convulsions (vide infra). In contradistinction to these authors E. R. Hoskins failed to show any constant effect of feeding thymus, and Swingle, taking two groups of individuals, frog larvæ, fed one, thymus extract and the other, liver, and could observe no difference in the growth or metamorphosis of either group. Uhlenhuth, in later papers, also divided his subjects (tadpoles) into two groups feeding one group thymus and the other worms. There was a differentiation, seemingly an inhibition of metamorphosis with those fed on thymus, but when he added to the thymus other energy-producing bodies, i. e., ordinary food substances, the inhibitory effects of thymus disappeared. Thus he showed clearly that thymus does not contain sufficient substances to maintain growth, and its effects when fed alone are due to malnutrition.

The inclusion, in the past, of the thymus among the internal secretory glands naturally intimates some close relationship between the latter and the former. Let us briefly discuss this phase of the question.

Henderson reports that castration in cattle is accompanied by hypertrophy of the thymus and Paton observed an unusually severe disruption of the whole organism when thymectomy and ganodectomy were both performed. Hewer's work intimates a compensatory effect between thymus and testis based on feeding experiments. Thymus-fed animals, he says, show a delay in development of testis (vide supra).

Wulzen obtained a retardation in growth of thymus in birds during pituitary feeding. Maxwell reports evidence against any relation between these two organs.

Uhlenhuth theorizes that the thymus produces a substance that tonically raises the sensitivity of the central nervous system and that the parathyroid secretion inhibits this action normally. His proof for this is as follows. In tadpoles there is no tetany in feeding thymus because the parathyroids have already developed, but in young salamanders, in which animal the parathyroids are de veloped late, thymus feeding does produce tetany.

Kahn wished to show a correlation between thymus and thyroid, using feeding experiments as evidence, but Uhlenhuth contradicts his results by stating

that "the inhibitory effect of thymus is not due to a specific inhibiting substance in the thymus, but to the absence from the thymus of a substance required to develop the thyroid to the secretory stage."

From the above we can conclude that the only relation which seems worthy of consideration is that between thymus and testis, but both these glands are normally so susceptible to any changes in the organism that more evidence is necessary to make their interrelation conclusive.

In considering the clinical evidence of thymus function it should be borne in mind that it is much more difficult to judge the value of clinical data because of the relatively few observations and because important information is often omitted. Hammar in an excellent and exhaustive article is convinced that the so-called "thymus death" is not of thymic origin. Herrick calculates that the thymus can not compress the trachea sufficiently to cause death by suffocation.

Hoxie details a method for percussing the enlarged thymus and claims to have relieved cases by thyroid and adrenal feeding. Haneborg reports cases of chorea in which he has obtained relief from convulsions after thymus feeding. He expresses doubt at the end of his paper as to his results, however.

Clinical symptoms may always be verified by x-ray, the technic of which is given in great detail by Cook and Simpson. Hewer caused atrophy of thymus by prolonged treatment. Friedland reports that x-ray treatment, as a routine measure, clears up "thymus diseases" dissipating the dyspnea, suffocation, cyanosis, stridor, etc., (?).

It is clear from a review of the literature bearing on the thymus that it is impossible to attribute any function to the gland. The work of Hammar who has recently made an exhaustive study of the thymus function both chemically and experimentally concludes with the remark that in his estimation the thymus is not an organ of internal secretion. And E. R. Hoskins considers that "the thymus functions as a lymphoid organ in infancy and childhood when a large number of lymphoid cells and leucocytes are needed to combat infections," a view which is upheld by a comparison of the graphs showing the curve of involution of the thymus. These closely approximate the curve of the decrease in the number of lymphocytes in the blood with increasing age.

Elsewhere the author states that "whatever the real function of the thymus, certain it is that its production of an internal secretion has not been proved." If we might be permitted to express an opinion, we would suggest that the thymus is a lymphoid organ like an enlarged tonsil which involutes when its presence is no longer necessary.

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TYPHOID AND PARATYPHOID FEVER AT MESVES HOSPITAL CENTER*

By Frank Mock, M.D., (Chicago, Ill.)
1st Lieut., M. C., U. S. A.

SUMMARIZING the work on enteric diseases done at the Center Laboratory of Mesves Hospital Center, France, the figures total as follows: stool examinations, 506; urine examinations, 402; blood cultures, 201. Of this number there were 37 positive stools, 6 positive urines, and 12 positive blood cultures, a total of 55 positive results on 45 patients. Two more were diagnosed at autopsy and from one of these the B. typhosus was isolated from the spleen and bile sac. The 45 positive cases were distributed as follows: stools 29, or about 64½ per cent; blood, 10 or 22⅕ per cent; urine, 6 or 13⅓ per cent. Twenty-one cases were clinically positive, but could not be proved by laboratory findings.

Twelve cases came to the Center which had been diagnosed at evacuation hospitals at the front.

Only six specimens of feces were found positive the second time and two the third time examined. Two blood cultures were found positive on the second examination. There were no duplications of positive urines. In one case the blood, feces and urine were positive, in five cases the blood and feces, and in one case the feces and urine.

The organisms isolated were B. typhosus in 38 cases, B. paratyphosus A in two cases and B. paratyphosus B in four cases. In one of our earliest cases we found the Shiga bacillus. In one case, sent in from Camp Hospital of the 85th Division at Sancerre, we got an atypical paratyphoid bacillus from a patient with

*Authority to publish granted by the Surgeon-General's Office, Washington, D. C.

clinical typhoid. This organism did not agglutinate in the patient's serum, or in our diagnostic sera. Probably the same organism was obtained from two carriers and a sample of milk at the hospital. Another atypical paratyphoid bacillus was obtained from a carrier in Evacuation Hospital No. 24. The B. paratyphosus B was obtained from a carrier at B. H. No. 54 who was relieved of his duties as mess sergeant. No cases could be traced to him. There were four organisms that were culturally typhoid but did not agglutinate. Nine organisms failed to agglutinate after having been previously positive, one failed to agglutinate when first isolated, but afterwards became positive, and one agglutinated twice, then failed to agglutinate, and again agglutinated when the fourth culture was isolated. The titer in the positive cases ranged from 1:400 to 1:25,800.

Agglutinations were done with typhoid and paratyphoid A and B organisms against the serum of sixteen men, four of whom were not patients but were used as controls. From the patients we obtained three typhoid, one para A and two para B reactions, and from the controls only one typhoid reaction. The titer of these sera which agglutinated ranged from 1.20 to 1:2560. The higher titered reactions corresponded with those of the organisms isolated from the patients' stools. Six patients and three controls were negative throughout. The reactions in general seemed to indicate that the patients' vaccination had run out, and the reading corresponded to those of Widal reactions in unvaccinated patients. The average time since the patient had received his vaccination was about one year.

Ten of the proven cases originated on the Verdun front, ten in various hospitals of this Center, four in the Argonne, one each at Marcony, Toul, and St. Mihiel. The origin of the others is not known to us. Of those which originated in this Center, probably half were infected before they arrived. Of the clinically positive cases, eight originated at Verdun, five at this Center, and one each in the Argonne, at Varennes and Dunn-sur-Meuse.

The atypical paratyphoid bacilli in some cultures resembled the B. typhosus, that is, they did not form gas, and fermented all sugars except lactose and saccharose, but in most cultures they resemble the paratyphoid bacilli, forming gas and failing to ferment dextrin as well as lactose and saccharose. They did not agglutinate in antiparatyphoid A or B sera, neither did they agglutinate in the patients' own sera. One man who harbored an atypical organism had clinical typhoid, one had no typhoid symptoms except diarrhea, which he had before he entered the hospital, and two others were true carriers and not patients.

CONCLUSION

These atypical paratyphoid organisms probably are involution forms of the true typhoid or paratyphoid bacilli. This presumption seems to be verified by the fact that some changed their cultural characteristics while others changed their agglutinating characteristics. These organisms, both typhoid and paratyphoid, after agglutinating with a high titer (in some cases as high as 1:6400), failed to agglutinate at all. The fact that one culture should show the characteristics of the B. paratyphosus and a transplant of the same culture the characteristics of the B. typhosus, and a third transplant revert back to that of the B. paratyphosus, demonstrates the very close relationship between these organisms.

THE ACTION OF ALCOHOL ON THE HEART AND RESPIRATION*

By Emry G. Hyatt, Chicago, Ill.

MOST of the experimental work on alcohol has been done on animals under an anesthetic. As is well known anesthetics act in a manner very similar to alcohol. For this reason the initial action of alcohol which is the only point when the action is disputed is obscured. In the investigation of alcohol, therefore, it is highly desirable to work without an anesthetic. To do this in an acceptable manner, a method must be devised which is painless and which will not excite the animal, since these conditions may be as obscuring as an anesthetic. Brooks[1] devised such a method for the study of alcohol without using an anesthetic. By introducing a pressure cannula into the neck of an animal under an anesthetic he was able to get tracings several days after the return to normal without apparent pain to the animal. While he states that there was no excitement and no pain connected with the recording of the tracings, one is doubtful about the degree of such absence, and must consider that while there was relatively little, it is still a question of relativity. This is especially true when the alcohol is administered with a hypodermic, or into a recently prepared gastric fistula. The same criticism may be applied to the work presented here although in the present case the circumstances are those in which alcohol has been given therapeutically, as a stimulant for heart or respiration.

The work corroborates the findings of Brooks and is recorded briefly.

METHOD

In order to eliminate the use of an anesthetic and at the same time to avoid pain when obtaining blood pressure tracings or when giving alcohol injections, the following method was employed: A large healthy dog was selected and anesthetized with ether and the spinal cord severed about the level of the 11th thoracic vertebra. This was done by making a short deep incision just to one side of the spine into which a probe was inserted between the 11th and 12th vertebræ thus completely severing the cord. The dog was then placed in a comfortable cage and allowed until the *next day* to recover. The operation was performed under aseptic conditions and no infection resulted which would have produced fever and other complications in a day or two afterwards.

The blood pressure was then recorded from the femoral artery by means of a mercury manometer and the alcohol was injected into the femoral vein.

One of the very important factors in obtaining a blood pressure tracing is that of keeping the animal absolutely quiet, and comfortable. In our case this was accomplished by feeding the dog before placing him upon the operating table, by carefully padding the table, and by covering his eyes when connecting him to the blood pressure apparatus or when giving him injections of alcohol.

The dog was entirely devoid of sensation in the hind legs and lay perfectly still during the operation and following the injection of alcohol. We feel con-

*From the Laboratory of Pharmacology, University of Illinois, College of Medicine, Chicago, Ill.
[1]Brooks: Jour. Am. Med. Assn., 1910, lv, 372.

fident, therefore, that the results obtained and reported below, were due specifically to the action of alcohol and not to outside factors such as ether, chloroform, movement, or excitement of the animal.

RESULTS

I. By Mouth.—Five c.c. of 25 per cent alcohol when given produced a slight rise in pressure followed by an immediate return to normal. That this rise was due to stimulation of the gustatory nerves and swallowing movements and not to any specific action of the alcohol was shown by the fact that a similar action was obtained by the same amount of normal one-tenth HCl.

II. By Injection.—Further proof that the rise in pressure was caused by local action and not to the action of the alcohol is shown by the fact that alcohol injected slowly into the femoral vein in doses of 5 c.c. and in concentrations from 5 per cent to 40 per cent produced no change in blood pressure. An amount equal to 60-75 c.c. of 40 per cent alcohol (the approximate strength of whiskey) was given during a period of one hour. To rule out the possibility of habituation playing a part in the results, initial doses in varying concentrations were given to different dogs with the same results.

III. By Infiltration.—Forty to 80 per cent alcohol was allowed to flow from a burette into the femoral vein of a dog at the rate of 2 c.c. per minute until the dog died. In different dogs this took place after the injection of from 50 to 150 c.c. of 40 per cent alcohol. The blood pressure in most instances remained constant almost until the time of death, at which point there was an abrupt drop.

When the alcohol was forced rapidly into the vein there was observed a fall in pressure followed by a rapid return to the normal. This was due perhaps to direct action on the central nervous system because when the vagi were cut a similar fall was not observed.

The effect of alcohol on the heart and respiration was also studied on the normal animal by counting. The animal was placed in a comfortable position and 40 per cent alcohol injected into the femoral vein. With careful work there is but the slight pain of the hypodermic needle. In this case the animal showed no detectable reaction to it. An anesthetic dose of alcohol may be given in this way without any apparent stimulation of the heart or respiration. The following experiment illustrates this:

Dog 25 lbs.	*Time*	*Normal Heart*	*Normal Respiration*
16 c.c. 40% alcohol injected.	11:00 to 11:03	94	17
		92	18
	11:15	78	15
	11:19	76	14
	11:26	74	15
	11:30	74	16
injected 10 c.c.	11:43		20
	11:47	88	
	11:55	74	15
	12:00		16
	12:10	74	16

Respiration increased in volume but not in number.
Heart is slowed.

In this experiment 26 c.c. of 40 per cent alcohol was injected into vein of leg without apparent effect on heart or respiration.

IV. By Stomach.—Forty per cent alcohol in doses varying from 5 to 16 c.c. when introduced slowly by means of a stomach tube produced no change in blood pressure.

Respiration.—No effect on rate was observed when the alcohol was injected gradually by the intravenous method or given by the stomach tube, although the respirations seemed deeper in quality. At the time of death a change was necessarily obtained.

We are confident that the volume of fluid introduced into the circulation was not sufficient to overcome any slight fall in pressure that might otherwise have been noted. To show this a control was made in which an equal amount of normal saline was injected in place of the alcohol without obtaining any change in pressure. To eliminate the possibility that the vaso-motor system might be unresponsive as the result of the severing of the spinal cord, adrenalin and nitrites were injected and characteristic curves obtained.

SUMMARY

From the results of the experiments performed above, we believe that alcohol has the following effects on heart and respiration when administered to an unanesthetized animal:

1. By mouth there is a rapid rise and an immediate return to normal. This is due to local action.

2. Intravenously.

(a) Given gradually in quantities sufficient to kill in one to two hours, there is no effect until just before death, when a rapid fall of pressure takes place.

(b) Given rapidly there is a sudden fall followed by an immediate return to the normal. There is no effect if the vagi are cut.

3. By stomach; when introduced by means of a stomach tube there is no effect.

4. When alcohol is introduced without excitement intravenously in the normal dog, there is no stimulation of the heart or respiration.

LABORATORY METHODS

THE EFFECT OF ADRENALIN ON THE BLOOD CATALASE*

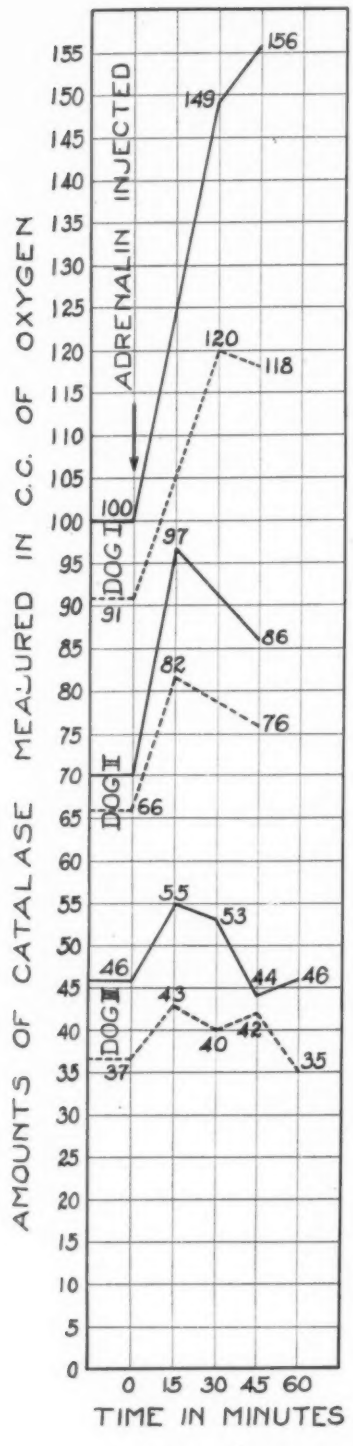
By W. E. Burge, Urbana, Ill.

As a result of the work of Blum,[1] Vosburgh and Richards,[2] Dreyer,[3] Oliver and Schaefer,[4] Cannon and de la Paz,[5] it is now considered that during combat the adrenals are stimulated to an increased output of adrenalin and that this produces a constriction of the small blood vessels of the abdominal viscera, thus increasing the blood supply to the heart, skeletal muscles, and nervous system; that it hastens the coagulation of the blood, and increases the output of sugar from the liver. It is evident that the purpose of diverting the blood from the abdominal viscera into the heart, skeletal muscles, and nervous system during combat is to render conditions more favorable for the increased action of those organs; that the hastening of the coagulation is to stop more quickly the bleeding from any superficial wound that may be inflicted, and that the flushing of the blood with sugar is to insure a plentiful supply of oxidizable material to the muscles. While the preceding explains certain phases of adaptation of the organism for combat, it does not explain how increased oxidation is brought about which gives rise to the energy for the fight.

We[6] had found that whatever increased oxidation in the body produced a corresponding increase in catalase, an enzyme possessing the property of liberating oxygen from hydrogen peroxide by stimulating the alimentary glands, particularly the liver, to an increased output of this enzyme, and that whatever decreased oxidation produced a corresponding decrease in catalase by diminishing the output from the liver and by direct destruction of the enzyme. It was found, for example, that the ingestion of food produced increase in the catalase of the blood parallel with the increase in oxidation, and that protein (meat), in keeping with its greater stimulating effect on oxidation, produced a larger increase in catalase than did fat or carbohydrate. On the other hand, narcotics decreased catalase parallel with the decrease produced in oxidation, chloroform being more effective in this respect than a less powerful anesthetic, such as ether. The object of the present investigation was to determine whether the introduction of adrenalin into the blood stream would stimulate the liver to an increased output of catalase. If this is found to be true, then it may be assumed that the increase in adrenalin during combat stimulates the liver to an increased output of catalase and that this, in turn, increases oxidation, thus giving rise to the energy for the fight.

The animals used were dogs. The adrenalin was introduced into the portal vein. The amounts will be given in the description of the individual experiments. The catalase was determined by adding 0.5 c.c. of blood to diluted hy-

*From the Physiological Laboratory, University of Illinois.



drogen peroxide at approximately 22° C. in a bottle and the amount of gas liberated in ten minutes was taken as a measure of the amount of catalase in the 0.5 c.c. of blood.

After exposing the jugular vein and opening the abdominal wall, with the use of ether anesthesia, 3 c.c. of a 1:1000 solution of adrenalin chloride were introduced into the portal vein in Dog III, Fig. 1; 5 c.c. in Dog II. In these two dogs, the solutions were injected as quickly as could conveniently be done. In Dog I, 10 c.c. of a 1:1000 adrenalin solution diluted to 50 c.c. were injected at a rate of approximately 2 c.c. per minute, requiring about 30 minutes for the injection. The catalase in 0.5 c.c. of blood taken directly from the liver and the jugular vein was determined before, as well as at fixed intervals after the injection of the adrenalin. The blood of the liver was collected from a superficial incision made in this organ. The results of the determinations are given in Fig. 1. The figures (0-155) along the ordinate represent amounts of catalase measured in cubic centimeters of oxygen, and the figures (0-60) along the abscissa, time in minutes. The solid line curves were constructed from data obtained from blood of the liver and the broken-line curves from the blood of the jugular vein.

It may be seen in Dog I, that previous to the introduction of the adrenalin into the portal vein, 0.5 c.c. of blood from the liver liberated 100 c.c. of oxygen from hydrogen peroxide in ten minutes, while 0.5 c.c. of blood from the jugular liberated 91 c.c. At the end of the injection of the adrenalin, which required 30 minutes, the catalase of the blood of the liver and jugular vein was greatly increased as is indicated by the increase in the amount of oxygen liberated from hydrogen peroxide. The catalase of the blood of the liver was increased to a greater extent than that of the jugular vein. This is taken to mean that adrenalin was stimulating the liver to an increased output of catalase. It may also be seen in Dogs II and III that a single injection of smaller amounts of adrenalin produced an increase in the catalase of the blood.

The introduction of adrenalin into the portal vein stimulates the liver to a

greatly increased output of catalase. This fact suggests that the increase in adrenalin during combat may stimulate the production of catalase and in this way aid in bringing about the increase in oxidation characteristic of great muscular exertion.

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A SIMPLE METHOD FOR DETERMINING THE REACTION OF FECES

By W. J. Bruce, New York City

While doing routine examinations of feces, I was impressed by the lack of a proper indicator for the reaction. No doubt, most technicians have at some time or other been confronted with a specimen the reaction of which it was impossible to determine correctly. The present method of using either litmus paper or litmus solution has, therefore, room for improvement.

When testing the reaction of feces that is very dark in color, using red litmus paper as the indicator, it is almost impossible to say whether the bluish color often obtained is a chemical reaction, or a stain from the specimen. Practically the same results are obtained with neutral litmus solution. The use of phenolphthalein as an indicator is also limited when testing feces.

Most textbooks recommend litmus paper. Faught states regarding the reaction of feces, "This is quite difficult to get with the ordinary paper. It can be easily obtained by dropping a little softened fecal matter into 5 or 10 c.c. of weak watery solution of neutral litmus solution, shaking it and noticing its color reaction." This method involves a most disagreeable piece of technic, that of getting the feces into a test tube and besides cleansing the glassware used for such an examination is objectionable to the person who takes care of such apparatus.

By the use of the method which I am about to describe, the reaction can be determined on the ordinary glass slide, or better still on a piece of white porcelain about 6 inches long and 1 inch wide. As soon as the reaction is decided, the slide is easily dropped in the disinfecting jar, thereby removing the menace of infection.

Prepare a 1 per cent aqueous solution of alizarin. Place two small drops of the indicator on a glass slide about one and a half inches apart. Dip a glass stirring rod into the liquid part of the specimen (or if the feces is formed, merely puncture the mass). By this means a sufficient amount of feces will be obtained for the test. Mix thoroughly in one of the drops, using the other drop

as a control. An alkaline reaction is indicated by a reddish violet to violet color, neutral no change, and acid to a light yellow color. The density of these colors, of course, will depend on the amount of acid or alkali present. By placing the slide upon a piece of white paper, the depth of color can be more easily determined. After a few observations, it is easy to detect any abnormality in the reaction. The use of the white porcelain is much more satisfactory, and is strongly recommended. A suitable opaque glass or white porcelain may be easily obtained at any local plate glass store, or at a sign writing shop.

During the last year or so, we were unable to procure a proper quality of red litmus paper to use in the examination of urine, but this indicator was substituted and gave satisfactory results. It can also be used in determining the reaction of human milk.

Although some biochemists and physiologists state that the reaction of feces has very little value, I believe a great deal of this feeling is due to the present unsatisfactory methods of obtaining it.

THE PRESERVATIVE FOR WASSERMANN REAGENTS

Chloroform the Best Preservative

By Clarence Emerson, M.D., Lincoln, Nebraska

ONE of the chief causes of difficulty in the performance of complement-fixation tests is the great tendency for decomposition of the reagents by the action of bacteria. The various sera employed furnish a splendid culture media for many saprophytic bacteria and their presence engenders putrefactive decomposition which inactivates certain sera and makes others not inactivated disagreeable to work with because of the odors. Some of the reagents in the various complement-fixation tests must be freshly prepared, some keep indefinitely under ordinary conditions and without special treatment, while others will undergo putrefaction and lose strength unless some measures are enforced for preservation. Since the alterations are usually dependent chiefly upon bacteria and putrefaction, most of the efforts to preserve the reagents have had as their object the retardation of bacterial growth. Two methods have been mainly followed:

1. Cold storage.
2. Chemical antibacterial agents.

It is my intention in this article to report the deductions from my experience with various methods of preserving certain of these reagents and especially to lay stress upon the great value of chloroform as a preservative for these sera.

I have not seen in the literature any previous reference to the use of chloroform for this purpose, and its value so far exceeds any other agent that I am familiar with that I believe a general recognition of its efficiency would be a

valuable addition to the technic of the complement-fixation tests. I shall consider separately the various reagents used in the tests.

1. ANTIGEN

Little need be said as to the preservation of antigen except in regard to the aqueous extract of luetic livers. Wassermann's original antigen was an aqueous extract and it was necessary to keep it in the ice chest and to avoid exposure to light. I have never used this form of antigen and since the alcoholic extracts are almost universally used and are preserved for an indefinite period because of the presence of alcohol, it seems that the preservation of antigen has reached a satisfactory stage of perfection.

2. RED CELLS

Red blood cells of the animal against whose blood an amboceptor has been developed are best preserved by keeping in cold storage after thoroughly washing with a salt solution that is one and one-half times as strong as normal salt solution. The cells, after washing until the supernatant liquid is clear, are finally centrifuged until sedimented and most of the supernatant fluid is poured off. To dry the cells completely and then reemulsify in salt solution increases fragility, while an excess of fluid favors autolysis. This is the usual recommendation with the exception of the strength of the salt solution. Often red cells from the sheep will hemolyze in normal salt solution, but will not break up in the stronger solution and the test is not in any way interfered with by the additional salt. I am also convinced that complement-fixation tests performed with red cells that are older than one week are unreliable. As soon as the red cell emulsion loses its bright red color and changes to a dark purple hue it is no longer serviceable for the test. If kept in the ice chest this usually will not take place before one week; however, if at room temperature it may occur in 24 hours. A few drops of chloroform retards this action, but reliance should be placed on freshness of the specimen rather than on any method of preservation known at the present time.

3. AMBOCEPTOR

An immune serum retains its amboceptor activity for a long time if kept in a suitable cold storage. The common ice chests of small size are usually not cold enough to prevent bacterial growth and putrefactive changes. This activity, however, can go on in an immune serum even to the extent of producing cloudiness and putrefactive odor without complete loss of its combining qualities. There is a gradual loss of strength and finally such weakness that the serum is discarded. It is in the preservation of amboceptor that I have been especially pleased with the use of chloroform because it prevents putrefaction, the serum remains potent for months with almost uniform strength and the disagreeable odors are never present. The chloroform evaporates soon after the amboceptor is diluted for test purposes and does not in any way interfere with the complement-fixation tests. I have treated separate parts of the same amboceptor with chloroform, thymol, phenol and other antiseptics and compared them with an untreated specimen kept under the same conditions for several months and

found that the chloroform preserved amboceptor much more potent and pleasant to work with than any other. In fact amboceptor with chloroform added may be kept at room temperatures for weeks without appreciable change. I usually add about 5 or 6 drops of chloroform to 10 c.c. of amboceptor, although I have made stronger proportions without any deleterious effect on the amboceptor or the test. The chloroform precipitates a whitish fine precipitate soon after addition, which does not carry with it any of the amboceptor qualities of the serum. It is not harmful to leave this precipitate and draw off the clear serum above as needed. From time to time if the chloroform seems to have evaporated as evidenced by the odor, I add more.

4. SUSPECTED AND CONTROL SERA

A most important consideration in complement-fixation tests is that of the handling of the suspected serum and control sera previous to the test. Of special importance are certain factors involved in the collection and mailing of blood to a distant laboratory. To collect blood in a bottle and send to a laboratory without special care as to the method will often make the test valueless. If the serum is not separated from the clot it may acquire antihemolytic qualities in 24 hours, and a complement-fixation test becomes impossible. Another important point is to be sure that the needle and syringe which may have been sterilized in boiling water just previous to use are thoroughly dry before blood is withdrawn because the water though small in amount may cause hemolysis and interfere with the test. Bacterial growth of course is detrimental and the addition of chloroform to the separated serum is a valuable procedure.

I would suggest the following instructions for physicians who desire to send blood to a laboratory for examination when the interval of time between securing the specimen and reaching the laboratory is apt to be 24 hours or more.

A. Collect 10 to 15 c.c. of blood in a clean dry homeopathic vial by inserting a sterile dry large-calibre hypo needle into a vein. The needles that come with record syringes are of such caliber that the blood will come through without suction by a syringe.

B. Immediately place the vial on its side with the mouth slightly elevated so the blood will clot with a proportionately greater surface. Separation of the serum is thus favored.

C. After a few hours when the clear serum has separated, draw it off with a clean, dry pipette and transfer to another vial. Add to this a few drops of chloroform.

In this form the serum may be shipped in an ordinary mailing case, without packing in ice and it will be serviceable for test purposes even after several days.

The control, normal, and syphilitic sera can be kept for a much longer period if chloroform is added.

5. COMPLEMENT (GUINEA PIG SERUM)

Guinea pig serum is probably universally used for complement and the necessity of having a source of supply is one of the trials of the Wassermann test. Various means have been suggested from time to time to prolong the period

of activity of complementary serum, but my own observation has led me to reject all of them. Diluting with highly concentrated salt solution, preservation in potassium acetate, drying on filter paper, etc., may prolong the activity to some extent, but I have not found any of them to sufficiently preserve complement to warrant their use. I am of the opinion that for dependable complement-fixation work a clear serum kept in cold storage and less than four days old, is an essential.

The fact should not be lost sight of that the distilled water that is used in the making of salt solution for the test serves as a medium for the growth of bacteria and molds and that some of these may have anticomplementary or antigenic properties and interfere with tests. The water should be freshly distilled.

To epitomize—the alcoholic extract of antigen keeps indefinitely. Red blood cells may be serviceable up to one week after collecting if sedimented in salt solution and kept in the ice box. Complementary serum must be not over four days old and kept in the ice box. The amboceptor, suspected sera, and control sera are much better preserved and are active for a greater period of time if a few drops of chloroform are added as a preservative. No test is of undoubted value if performed on sera kept in contact with the clot longer than 24 hours.

As confirmatory of the value of chloroform in preserving these sera and its innocuousness in the performance of the test I will say that Dr. Miles Brewer, of Lincoln, who was laboratory technician in charge of Wassermann work at Base Hospital No. 49 in France reported to me that he had used my method of chloroform preservation of amboceptor and sera throughout an extensive experience there with very satisfactory results.

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EDITORIALS

Some Recent Work on the Control of the Respiratory Center

FROM the moment the animal is born until death, breathing proceeds with a rhythm which is occasionally broken for brief periods of time by voluntary holding of the breath or by participation of the respiratory musculature in the various expulsive acts of the body, or in phonation and singing. The respiratory movements involve the harmonious activities of greatly diverse muscular groups, some of them contracting, while others relax, but always in so perfect a synchronism that the movement produced alters the capacity of the thorax in the manner which will most effectively ventilate the pulmonary alveoli. During inspiration, for example, the muscles which elevate the thoracic cage and those which depress the diaphragm contract at the same time that the muscles of the abdominal walls relax to make more room for the depressed viscera.

The excitatory or inhibitory nerve impulses which control these movements come finally, of course, from the cells of the lower neurones and these are scattered along the cerebrospinal axis from the level of the nerve centers for the muscles of the alæ nasi in the pons to those of the abdominal muscles in the lumbar region of the spinal cord. But it is plain that these centers can not in themselves be more than local executives for a higher command which must have

its headquarters in some more or less localized group of nerve cells. This chief respiratory center, as it is called, is usually considered to be situated in the medulla oblongata but there is good reason for believing that its upper limits extend for some distance into and perhaps beyond the pons.

It is clear that the fundamental problems of respiratory control must be directed to ascertain the conditions which excite or alter the activity of this center, and it is around this question that much important work has been contributed during recent years, particularly by the Oxford School of Physiologists led by J. S. Haldane[1] and the Copenhagen School led by August Krogh.

There are in general two ways in which the activities of a center might be caused to alter. These are by changes in the chemical composition of the blood supplying it and by nerve impulses derived from other parts of the nervous system.

Confining our attention for the present to the former class of influences, it may be said that tendency is to consider the hydrogen-ion concentration (C_H) of the blood that bathes the center as chiefly responsible. According to this view alterations in C_H furnish the respiratory hormone.

While there can be no doubt that the respiratory center is extremely sensitive to the slightest changes in C_H of the blood, indeed, it is probably safe to say that there is no more sensitive indicator of changes in C_H than the respiratory center, yet many serious objections can be raised against the view that the ordinary physiologic alterations in respiratory activity are brought about in this way. Because of the fact that the center is sensitive to changes in C_H which can not be measured by any known laboratory method it is impossible to furnish direct proof for or against the hypothesis. All the evidence is of an indirect nature and in many cases it is dependent upon assumptions and analogies which may possibly be erroneous.

It has long been known that respiratory activity can be excited by experimentally raising C_H of the blood, through the injection of mineral acids intravenously, but this does not necessarily mean that ordinary (physiologic) alterations in that function are due to the same cause. A great part of the indirect evidence is based on the observation that the tension of carbon dioxide (CO_2) in the blood bears a relationship to C_H of this fluid and to the degree of pulmonary ventilation. This is the case because CO_2 in solution is a weak acid and therefore cooperates with the other acids of blood to maintain C_H. It possesses one advantage over the other acids in that it is volatile and consequently can readily be got rid of through the alveoli. Whenever, therefore, there tends to be an increase in C_H of the blood some of the CO_2 which is in simple solution in the plasma is got rid of so that the tension declines and the percentage of CO_2 in the alveolar air becomes lower. The tension of CO_2, in other words, declines so as to make room in the blood for other acids. When the adjustment is perfect, the condition is often called *compensated acidosis,* but when there is too much fixed acid, so that C_H is slightly raised, it is called *uncompensated acidosis.* In the former case there is no respiratory disturbance when the person is at rest, but such is readily induced by the slightest exertion because there is a deficiency of basic substance available in the blood and tissues to combine with the

increased CO_2, and other acids, produced by the active muscles; the *buffer action* of the blood is said to be depressed. In the latter case, on the other hand, there is hyperpnea even at rest.

The H-ion concentration may obviously be raised by a process which is fundamentally the reverse of that just considered; namely, by an increase in the CO_2 tension while the other (fixed) acids of the blood remain constant. In this case acidosis will occur and there will be hyperpnea along with a higher percentage of CO_2 in the alveolar air; this condition is styled carbonic acid[2] and it occurs in uncompensated cardiac cases and to a certain extent in asphyxial conditions and during strenuous muscular exertion.

In all of the foregoing instances the interpretation of the respiratory excitement which has almost universally been adopted is that C_H of the blood has become raised, but if we pause to consider all the facts, it will be seen that the conclusion is by no means inevitable. It may as well be that it is the free CO_2 as such, or more precisely the anion HCO'_3 (for $H_2CO'_3$ will dissociate into $H \cdot \rightarrow HCO'_3$) that is the really important hormone instead of the cation $H \cdot$. In the cases of carbonic acid acidosis this is easy to understand; in cases of uncompensated acidosis it may be explained if we remember that there is now no sufficient amount of base to take up and fix as carbonates the CO_2 as it is produced, so that the free CO_2 in the cells of the respiratory center, as in other cells, is not adequately removed. There is a certain amount of experimental support for this view of which the following may be cited: Hooker, Wilson and Connett[3] succeeded in retarding death in the basal regions of the brain sufficiently so that respiratory movements were still present and they found that these movements became more markedly excited at a certain C_H of the perfusion fluid when the acid present was mainly H_2CO_3 than when it was any other acid. R. W. Scott[4] found that the respiratory movements in decerebrate cats were increased in proportion as the percentage of CO_2 in the respired air was raised. Examination of the arterial blood by the colorimetric method showed that C_H also became increased under these conditions, an observation which in itself, might support the view that it is really elevation of C_H that furnishes the stimulus to the respiratory center. That this is not the sole, if even the main, stimulus was shown in further experiments in which amounts of alkali were first of all injected intravenously so that decided depression in C_H of the blood was established. On now causing these "alkalosis" animals to respire in CO_2-rich atmospheres it was found that the respirations were excited practically to as great a degree as in the animals with normal C_H; although this became raised, it had not nearly attained the level at which it stands in normal blood even when very marked hyperpnea was present. Increase in CO_2 tension, quite independently of increase in C_H above the physiologic level, had quite clearly afforded the stimulus to the center. It will be necessary to repeat the observations by the use of the electrometric method for measuring C_H of the blood.

If further investigation should confirm the hypothesis that CO_2 tension is a more effective stimulus for the respiratory center than C_H it will mean that, unlike the rhythmic action of the heart which is highly susceptible to cations the rhythmic action of the respiratory center is so to anions. The excitability of the

respiration center towards certain concentrations of the CN-ion is of great interest and significance in this connection although the action is differently explained by its discoverer, Loevenhart. The rhythmic contractions of the isolated small intestine are also highly susceptible to the influence of anions.

Apart from their theoretical interest the foregoing facts are of undoubted practical importance since they show that a certain tension of CO_2 must exist in the blood which bathes the respiratory, and very likely other centers, in order that the physiologic activity may be maintained. The observations recall the old hypothesis of Mosso that certain perversions of physiologic function may occur when the tension of CO_2 is subnormal (acapnia).

One of the most important questions in connection with the hormone control of the respiratory center concerns the influence of a deficiency of oxygen in the inspired air. It has long been known that dyspnea usually supervenes in atmospheres which are decidedly deficient in this gas. There are two well-known types of observation which illustrate this fact. The first of these is the laboratory experiment in which a person is caused to breathe in and out of a large spirometer or rubber bag provided with soda lime to absorb carbon dioxide, dyspnea develops, becoming very marked when the oxygen has fallen below 14 per cent. The other is afforded by watching the respiration at high altitudes, it is hyperpneic so that the alveoli are more thoroughly ventilated and the supply of oxygen in them becomes more frequently replenished in order to compensate for the decreased percentage in the atmosphere. There is therefore no doubt that deficiency of oxygen excites the respiration; the question is whether the stimulus is the oxygen deficiency *per se* or whether it is dependent upon some condition which is set up by this deficiency. In considering this question it is important to distinguish between extreme and moderate degrees of oxygen deficiency. When it is extreme the respiratory center, like all other centers, becomes depressed apparently without any preliminary stimulation, and breathing ceases. Such a condition occurs when the blood supply to the medulla is seriously interfered with and in cases of respiration in poisonous gases, like carbon monoxide or methane. A similar depression of the respiratory center due to oxygen deficiency may possibly be the cause of death in such diseases as acute pneumonia and edema of the lungs. It is of decided practical value to know that it is possible to restore a center rendered inactive through deficiency of oxygen by increasing the percentage of this gas in simple solution in the blood supplying the medulla. We have observed this restorative power of oxygen inhalations very strikingly in the case of decerebrate cats (Fraser, Lang and Macleod). These animals breathe with perfect regularity as long as there is an adequate supply of oxygen to the medulla, but if this be curtailed, as by temporarily clamping the vertebral arterioles, the respirations gradually cease but return immediately the circulation is restored. Sometimes, especially when the arterio corpora quadrigemina are destroyed, the breathing in the decerebrate animals becomes irregular and gradually ceases entirely, though the heart is still beating and there is a fair arterial blood pressure. In such cases normal respiration is promptly restored by raising the partial pressure of oxygen in the alveolar air which is most conveniently done by introducing pure oxygen low down in the trachea through a

catheter and interrupting the stream rhythmically at about the same rate as the animal breathes. The restored breathing continues for some time after discontinuing the oxygen inhalations.

In view of the results it is possible to explain the beneficial effects which often follow the administration of oxygen in cases of pneumonia, in coal gas poisoning, etc. The inhaled oxygen raises the tension of this gas in the alveolar air so that a sufficient amount of it becomes dissolved in the plasma to keep the center alive, independently—in the case of CO-poisoning at least—of the formation of more oxyhemoglobin. That nerve centers and other tissues can be kept alive by physiologic saline in which excess of oxygen is dissolved is a well-established fact and it should be our aim, when treating cases of asphyxia, to raise the partial pressure of this gas in the alveolar air as high as possible. The dissolved oxygen supplied to the centers in this way must be maintained until the mechanism of which the supply is normally ensured, namely, by dissociation of the oxygen bound to hemoglobin, has been restored to normal. The resuscitation afforded by increasing the percentage of oxygen in the alveolar air, although it can only be temporary, may serve to tide over a crisis and so permit the normal mechanisms by which oxygen is transported to the tissues to become restored.

With regard to the second method of respiratory control, namely, that through afferent nerve impulses only a few of the most outstanding facts can be referred to here. The older work seemed to show the most important of these impulses to be transmitted to the center along the vagus nerves and the hypothesis was formulated that the rate of the respiratory movements depends fundamentally on the fact that towards the end of each inspiration an impulse set up by the distention of the alveoli, is transmitted to the center where it inhibits the rhythmic discharge and so brings on an expiration. Without these inspiration inhibitory impulses respiration is much slower and deeper than normal. There is a growing mass of evidence which goes to show that these afferent impulses, as well as others derived from the afferent nerves of the thoracic parietes (including muscular sense impressions) are important in harmonizing the action of the respiratory musculature much in the same way that afferent impulses from the extremities are important in the synthesis of the complicated muscular activities necessary for the maintenance of the erect posture and for locomotion (Pike,[5] Boothby and Berry[6]).

That the respiratory center is influenced by afferent impulses which are set up by the degree of distention of the lungs has been shown in experiments by Lois Fraser, Lang and Macleod.[7] The experiments were performed on decerebrate cats. When these animals were caused to breathe into wide-bore tubing provided with bottles containing soda lime to absorb the carbon dioxide it was found that the respiratory volume became markedly increased while there was still practically no reduction in the percentage of oxygen in the inspired air. This evidence, furnished by registration of the volume of respired air (by a Gad-Krogh spirometer) was confirmed by observing the behavior of the respiratory quotient of the alveolar air. Immediately the breathing into the tubing was started the quotient rose considerably. sometimes to 2.0, indicating that CO_2

was being washed out of the blood by the more thorough ventilation of the alveoli. When the animal was allowed to breathe in outside air again the breathing respiratory volume quickly returned to the normal and the respiratory quotient fell to a very low level showing that the blood was now taking up the CO_2 it had lost.

This experiment recalls the experience of every one who has tried to breathe through tubing into a spirometer or gas absorbing apparatus; a certain degree of hyperpnea is always set up which is usually attributed to a conscious sense of effort. But the foregoing observations show clearly that the reaction is independent of the higher centers and that it must be purely reflex through the respiratory center, the afferent stimulus being the state of distention of the lungs or thorax. The stimulus which excites the hyperpnea may persist indefinitely or it may subside after a time. In cases in which it does not subside it will lead to an overventilation of the alveoli and consequently to a depletion of the free CO_2 of the blood (acapnia). It is possible that it is because of this condition that prolonged respiration through a gas mask or into a respiratory apparatus frequently becomes unbearable on account of the sense of bodily discomfort which develops (mask staleness).

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—*J. J. R. M.*

Hemoglobin

THE essential substance in the blood, so far at least as oxygen is concerned, is hemoglobin. This substance is the respiratory material of the body, the substance upon which depends completely the presence of oxygen when it is needed, and in the amounts in which it is needed. Absence of hemoglobin is not compatible with life, and diminution of it produces disease, as is so well known from studies of chlorosis, and other forms of anemia.

If one stops to think of the remarks of Barcroft he will at once be impressed with the meaning of the thing. "In warm-blooded animals, muscle, when working at its full power, uses up its own volume of oxygen in about ten minutes. This oxygen is carried to it by the hemoglobin of the blood—a substance so rich in oxygen that a relatively small quantity of blood satisfies the need of the muscle. Were it not for this pigment some 200 c.c. of fluid would have to be circulated through every gram of muscle in ten minutes of time. To put the matter in another way, blood carries about 40 times as much oxygen as the same volume of plasma. Therefore, to convey as much oxygen around the body as is carried by the blood, would, in the absence of hemoglobin, demand 150 kilos of plasma, or perhaps more. The contents of the vascular system would therefore

amount to twice the present weight of the body. The body would, in short, be unable to cope with the weight of its own blood. The whole basis of its economy therefore hinges upon the accidental possibility of the occurrences and properties of hemoglobin."

Since hemoglobin is the essential oxygen carrying substance of the body, loss of any proportion of it or any interference with its function must have the most far-reaching results. For the most part the recognized and appreciated results of hemoglobin loss, in amount or activity, are grouped with the anemias.

Now anemia, the word, literally means without blood, and blood can be lost or reduced in a variety of ways. For instance, there may be interference with the production of the red cells of the blood—the cells which contain the hemoglobin. Hemoglobin itself may not be found in sufficient amount because of failure of the supply of iron in the diet, or a breaking down of the mechanism by which it is formed. Red blood cells may be produced in sufficient numbers to satisfy the needs of the economy, but they may be destroyed by parasites, or by poisonous substances, malaria on the one hand; quinine on the other. In any case, however, the fact of importance in this group of anemias is that there is not enough hemoglobin to satisfy the demand for oxygen by the body.

But besides these hemoglobin anemias, there is probably another group of conditions in which despite a quantitatively sufficient amount of hemoglobin, oxygen is not carried in amounts compatible with health. Such conditions are those in which the hemoglobin is not able to combine sufficient oxygen, even though the supply of that gas is normal. Perhaps the simplest example of such a condition is that due to cold—simple chilling of the body. Other examples, it may be discovered, may be due to abnormal salt concentrations of the plasma, perhaps even to unusual amounts of a single salt. Such conditions are not well defined at the present time because too litttle is known concerning the special effects of salts in the blood. What little is known is that the affinities of hemoglobin for oxygen are profoundly modified by temperature and by the general salt content of the plasma. It is also known that the dilution of the blood has no effect on the oxygen capacity,* i.e., mere plethora does not modify the amount of oxygen the blood can carry. The reaction of the blood is we know of fundamental importance in modifying the oxygen supply.

Temperature acts in reducing the percentage saturation of hemoglobin, and in increasing the reduction. For instance, Barcroft gives the following figures:

Temperature	16°	24°	32°	38°	49°
Percentage saturation	92	71	37	18	6

A similar experiment, at a much higher oxygen pressure, with a hemoglobin solution made in a different way but also dialyzed, yielded the following results:

Temperature	16°	25°	32°	38°
Percentage saturation (observed)	96	89	77	52
Percentage saturation (calculated)	97	89	74	54

*Barcroft, p. 25 (Burns' figures):

Degree of Dilution of Blood	O-capacity by Absorption Method	O-capacity by Ferricyanide Method
Undiluted	17.6%	17.4%
5 times	17.6%	17.5%
7 times	17.8%	17.1%

In bringing about reduction, Barcroft says, at the conclusion of an experiment, that while "at 18° C. 35 minutes were required for the reduction of the hemoglobin from 100 per cent to 94 per cent saturation, at 38° C. it only required 7.5 minutes to reduce it from 94 per cent to 77 per cent."

It appears from these facts that the amount of oxygen which hemoglobin can take up, and the amount and rapidity with which it can give up combined oxygen varies with the temperature of the body, a state of affairs that must have some important significance in fevers.

But, besides the temperature, there is another factor which is essential in regulating the transfer of oxygen; namely, the salt content of the blood. This is what might be expected from the fact that hemoglobin is a colloid, and from what we know of the effects of electrolytes on colloids. From experiments it has been found that potassium salts are partially efficient in causing hemoglobin to absorb oxygen (Macleod, p. 386). In fevers and other conditions associated with loss of water, the salt concentration of the body may be of the greatest import and the mere loss of a seemingly unimportant amount of water may react in greatly reducing the necessary oxidations of the body. Especially may this be true when with the salt effects are united those due to heightened temperature.

Finally there is the factor of acidity—of hydrogen-ion concentration—which has a tremendous influence on the activities of hemoglobin. The effect of increased acidity of the solution is to lessen the effective concentration of the oxygen in the solution which contains the hemoglobin. The concentration of free carbonic acid in the solution, necessary for production of a measurable change in the affinity of hemoglobin for oxygen amounts to something of the order of one part in one hundred million (Barcroft, p. 53), and lactic acid acts in precisely the same way.

These three factors—temperature, electrolytes, and reaction—are of the utmost importance in determining the direction of disease, and they are in no way less important in indicating the direction of therapeusis. A single example of what might happen in the body, with respect to its internal respiration, may be given as follows:

The temperature of the body rises, and because of this, the blood (hemoglobin) is able to combine with less oxygen in the lungs. Because of the increased temperature, metabolism is increased, and the products of metabolism accumulate, and these are not promptly and efficiently removed because of the decreased oxygen in the blood. The products of metabolism are not uncommonly acid, and therefore those remaining in the tissues cause the latter to hold water and to take more water for the circulating fluids. The result of this is that the plasma loses water and its salts become more concentrated, a state of affairs that leads to still further reduction of the oxygen-combining power of the hemoglobin. At the same time the reaction of the blood (the H-ion concentration) is increased and again a more or less serious state of affairs arises, depending upon the degree of the process.

The above verbal scheme is given merely because it is suggestive of what might happen with reference to the hemoglobin alone. If the scheme is useful from the side of treatment it means first, that in fevers water is primarily necessary, and that second, alkalies are valuable. The one makes evaporation from

the body possible, and this in addition to radiation, serves to reduce the temperature. At the same time the concentration of the plasma tends to be reduced. The other acts to reduce the available acidity of the blood. Both together tend to act to increase the combining power of hemoglobin for oxygen, and the oxygen in its turn is the fundamental agent in getting rid of waste products of metabolism.

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—*P. G. W.*